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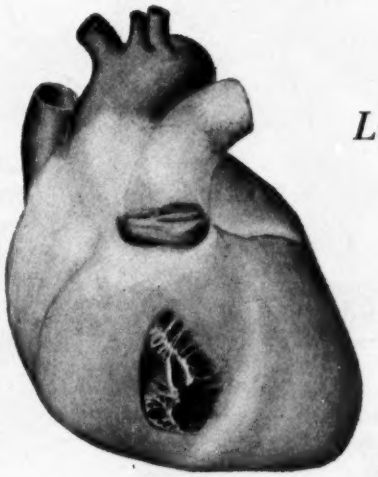

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1. Kroop, I. G., Heffer, E. T., Turin, R. D., and Slater, S. R.: Scientific Exhibit Graduate Fortnight, New York Academy of Medicine, Oct. 6, 1952.
2. Bunim, J. J., Kuttner, A. G., Baldwin, J. S., and McEwen, C.: *J. A. M. A.* **150**: 1273–1278, Nov. 29, 1952.

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*Jeans, P. C., and Marriott, W. McKim: Infant Nutrition, ed. 4, St. Louis, C. V. Mosby Co., 1947.

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Bibliography:

1. Frank, P.F., Wilcox, C., and Finland, M.: In Vitro Sensitivity of Coliform Bacilli to Seven Antibiotics, J. Lab. & Clin. Med. *35*:188 and 205, 1950.
2. Jawetz, E. and Coleman, V.R.: Laboratory and Clinical Observations on Aerosporin (Polymyxin B), J. Lab. & Clin. Med. *34*:751, 1949.
3. Pulaski, E.J. and Rosenberg, M.L.: Use of Polymyxin in Gram Negative Urinary Tract Infections, J. Urol. *62*:564, 1949.
4. Kagan, B.M., et al.: Polymyxin B and Polymyxin E, J. Lab. & Clin. Med. *37*:402, 1951.
5. Lieberman, D. and Jawetz, E.: Treatment of Chronic Shigella Infections in Children with Oral Polymyxins, Pediatrics *18*:249, 1951.
6. Jawetz, E.: Infections with Pseudomonas aeruginosa Treated with Polymyxin B, Arch. Int. Med. *89*:90, 1952.

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Gunther, M.: Brit. J. Nutrition 6 (No. 2): 215, 1952.

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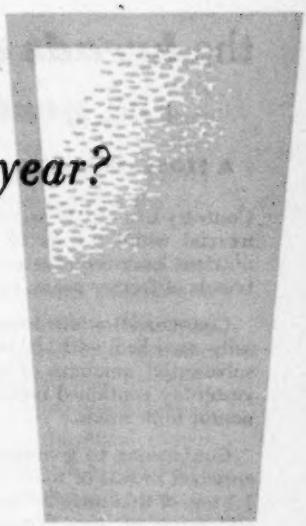

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*Bull. Johns Hopkins Hosp. 87:569, 1950.
†J.A.M.A. 146:35, 1951.

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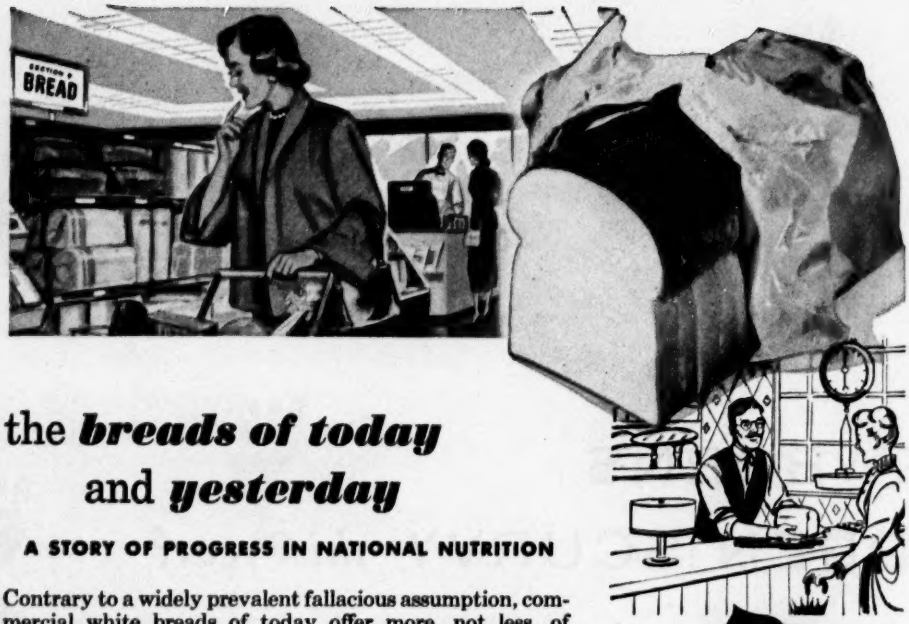

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1. Flour and Bread Enrichment, 1949-50: Prepared by The Committee on Cereals, Food and Nutrition Board, National Research Council, Washington, D.C., 1950.
2. Geddes, W.F.: Cereal Chemists Guard Nutrition, Agricultural and Food Chemistry *1*:38 (Apr.) 1953.
3. Bakery Products; Definitions and Standards of Identity, Federal Register *17*:4453 (May 15) 1952.
4. Sherman, H.C.: Chemistry of Food and Nutrition, ed. 8, New York, the Macmillan Company, 1952, p. 599.
5. Goddard, V.R., and Marshall, M.W.: The Calcium Content of Commercial White Bread, United States Department of Agriculture, Technical Bull. No. 1055, 1952.

   Crespo, S., and Bradley, W.B.: Calcium and Milk Content of Commercial White Bread. Report by the Laboratories of the American Institute of Baking, Feb. 28, 1950.

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American Journal of Diseases of Children

VOLUME 85 JUNE 1953 NUMBER 6

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FUNCTION RECOVERY PATTERN IN ACUTE RENAL FAILURE FOLLOWING INGESTION OF MERCURIC CHLORIDE

S. A. KAPLAN, M.D.
AND
SAMUEL J. FOMON, M.D.
CINCINNATI

THE CHARACTERISTIC renal lesion produced by mercuric chloride has been described as being confined largely to the proximal tubule.[1] Large doses of mercury tend to produce necrosis extending the whole length of the proximal tubule from the glomerulus to the descending loop, while smaller doses appear to affect selectively the more distal portions of the proximal convolution and its medullary portion.[2] Subnecrotizing doses may produce no more than swelling of the epithelium, presumably, in the more distal segments of the proximal nephron.

Recently Oliver and associates [3] have drawn attention to a second type of tubular lesion which may be found in cases of poisoning with corrosive mercuric chloride and which is indistinguishable from that found in shock-like states such as following crushing injuries and transfusion of incompatible blood. The second type of lesion differs from the nephrotoxic lesion found uniformly in the proximal nephron; it consists of a disruption of the continuity of the tubule including the basement membrane and may be found anywhere from the proximal to the distal convolutions. The sequence of events in the pathogenesis of renal failure as envisaged by Oliver and his associates is as follows: The initial lesion produced by poisoning with mercury consists of necrosis of epithelium in the proximal tubule or "diffuse nephrotoxic proximal damage." If the lesion is severe, there follow dehydration and circulatory collapse which result in renal ischemia and disruption of the basement membrane or "tubulorhexis." With ischemuric episodes [4] following

From The Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati College of Medicine.

1. Suzuki, T.: Zur Morphologie der Nierensekretion unter physiologischen und pathologischen Bedingungen, Jena, Germany, Gustav Fischer, 1912. Edwards, J. G.: The Renal Tubule (Nephron) as Affected by Mercury, Am. J. Path. **18**:1011, 1942. Simonds, J. P., and Hepler, O. E.: Experimental Nephropathies: A Method of Producing Controlled Selective Injury of Renal Units by Means of Chemical Agents, Arch. Path. **39**:103, 1945.

2. Simonds, J. P., and Hepler, O. E.: Experimental Nephropathies: Summary of Experiments on Dogs, Quart. Bull. Northwestern Univ. M. School **19**:278, 1945.

3. Oliver, J.; MacDowell, M., and Tracy, A.: The Pathogenesis of Acute Renal Failure Associated with Traumatic and Toxic Injury: Renal Ischemia, Nephrotoxic Damage, and the Ischemuric Episode, J. Clin. Investigation **30**:1305, 1951.

4. The term "ischemuric episode" was coined by Oliver to describe an "episode of renal ischemia resulting in ischuria." In the light of current knowledge this new term should replace "lower nephron nephrosis."

crushing injuries and transfusions of incompatible blood, the tubulorhectic lesion is the primary one and is a consequence of the shock and renal ischemia which are characteristic of these states. Disruption of the basement membrane "is the factor which prevents repair, for not only is there no directing surface on which regenerating epithelial cells 'creep' to reform the tubule but the gap in the tubule wall is invaded by granulation tissue which fills and obliterates the tubule lumen.[3]"

Anuria may result either from arrest in the formation of glomerular filtrate or from back diffusion of tubular fluid into the peritubular spaces through structural defects in the tubular system. Direct evidence in favor of the latter hypothesis was provided by Richards,[5] who noted the absence of formation of urine in the frog kidney poisoned by mercuric chloride, in spite of normal glomerular filtration. Indirect evidence of abnormal permeability of the tubules in acute renal injuries, produced by a variety of toxic agents or following shock-like states, has been presented by several observers. Such evidence has consisted, first, of the recovery in the urine of substances such as paraaminohippurate[6] or iodopyracet (Diodrast)[7] in quantities smaller than those calculated to have been filtered at the glomeruli. Since these substances are known not to be reabsorbed by the tubules, it has been deduced that their loss from tubular fluid has resulted from abnormal tubular permeability. Second, evidence has been presented that there is a differential permeability to substances which are not normally reabsorbed by the tubules. In the normal dog both creatinine and inulin are filtered at the glomerulus, and neither substance is absorbed by the tubules, so that the ratio of the concentrations of these two substances in the urine is identical to that existing in the plasma. In dogs poisoned with uranyl nitrate, however, inulin and creatinine appear in the urine in quantities indicating that there has been greater back diffusion of creatinine (molecular weight 113) than of inulin (molecular weight about 990).[8]

Because of the back diffusion of paraaminohippurate across the tubular wall, it is clear that this substance cannot be used for determination of renal blood flow as in routine clearance measurements. To determine the blood flow accurately, it is necessary to obtain specimens of both arterial and renal venous blood and to apply the Fick principle

$$\text{Renal plasma flow/min.} = \frac{\text{Paraaminohippurate excreted/min.}}{A - V}$$

where A and V represent paraaminohippurate concentrations in arterial and renal venous blood, respectively. With this technique inulin, diodrast, creatinine, or paraaminohippurate may be used to measure renal plasma flow.

5. Richards, A. N.: Direct Observations of Change in Function of Renal Tubule Caused by Certain Poisons, Tr. A. Am. Physicians **44**:64, 1929.

6. (*a*) Redish, J.; West, J. R.; Whitehead, B. W., and Chasis, H.: Abnormal Renal Tubular Back-Diffusion Following Anuria, J. Clin. Investigation **26**:1043, 1947. (*b*) Marshall, D., and Hoffman, W. S.: The Nature of the Altered Renal Function in Lower Nephron Nephrosis, J. Lab. & Clin. Med. **34**:31, 1949.

7. Bobey, M. E.; Longley, L. P.; Dickes, R.; Price, J. W., and Hayman, J. M., Jr.: Effect of Uranium Poisoning on Plasma Diodrast Clearance and Renal Plasma Flow in the Dog, Am. J. Physiol. **139**:155, 1943.

8. Richards, A. N.; Westfall, B. B., and Bott, P. A.: Inulin and Creatinine Clearances in Dogs, with Notes on Some Late Effects of Uranium Poisoning, J. Biol. Chem. **116**:749, 1936.

The interpretations of the morphologists (that oliguria and anuria in acute renal failure are the consequences of renal ischemia which produces reduction in glomerular filtration and, perhaps of greater importance, tubular disruption) receive considerable support from functional studies of tubular permeability and renal hemodynamics. With the possible exception of uranium poisoning,[9] these studies reveal marked impairment of renal blood flow and filtration rate even for periods extending up to several weeks after the production of the initial insult.[10] Thus there appears to be a valid basis for the hypothesis that renal ischemia and tubular disruption are important pivots about which the pathogenesis of the syndrome of acute renal failure revolves.

While much attention has been focused on measurements of hemodynamics, comparatively little is known about the function of the kidneys with respect to their reabsorptive, secretive, or concentrating powers during the early phases of recovery from the initial trauma. Isolated measurements have been reported sporadically, but with the notable exception of the studies of Bull and associates[11] there appears to have been no systematic approach to analysis in detail of the recovery of renal tubular function. These authors drew attention to the considerable impairment in tubular handling of sodium, chloride, urea, creatinine, and glucose which occurs in renal injuries produced by a wide variety of etiologic agents. By serial studies they traced the gradual return of these functions and subdivided the phases of recovery according to the degree of residual tubular impairment. They also drew attention to limits which the tardy recovery of renal function should impose on the quantity and type of fluids administered parenterally during the phase of recovery.

We have had a recent opportunity to extend these observations. The study of a child in whom an ischemuric episode developed after the ingestion of mercuric chloride and in whom return of renal function was fairly complete has permitted the recognition of a distinct pattern of recovery of normal function. It was possible to detect those changes in renal function reflecting recovery of glomerular function as distinct from those changes reflecting recovery of function of the proximal tubules. These changes, in turn, could be distinguished from those indicating the return of distal tubular activity. The sequence of events which occurred in this case correlates closely with a presumptive structural path of healing based on the knowledge of the morphologic abnormalities present in this disease. From an analysis of the data presented by Bull and associates[11] it seems likely that this pattern of recovery is not limited to the case described here but may occur also in cases of recovery from acute renal injury following a variety of etiologic agents.

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9. Sirota, J. H.: Carbon Tetrachloride Poisoning in Man: I. The Mechanisms of Renal Failure and Recovery, J. Clin. Investigation **28**:1412, 1949.

10. Simonds and Hepler.[2] Marshall and Hoffman.[6b] Sirota.[9] Corcoran, A. C.; Taylor, R. D., and Page, I. H.: Acute Toxic Nephrosis: A Clinical and Laboratory Study Based on a Case of Carbon Tetrachloride Poisoning, J. A. M. A. **123**:81, 1943. Schou, P.: Experimental Studies on Kidney Function During Sulphate Diuresis: Investigation on Kidney Function in Rabbits with Chronic Tubular Nephritis, Acta physiol. scandinav. **7**:200, 1944.

11. Bull, G. M.; Joekes, A. M., and Lowe, K. G.: Renal Function Studies in Acute Tubular Necrosis, Clin. Sc. **9**:379, 1950.

REPORT OF A CASE

A 4½-year-old boy was admitted to the hospital on Feb. 18, 1952, because of the ingestion of two 0.5 gm. tablets of mercuric chloride one hour previously. A physician had washed out the stomach and had administered apomorphine about 30 minutes prior to admission.

On admission the boy was restless, apprehensive, and pale and was vomiting blood-stained mucoid material. The temperature was 97 F., the pulse rate 150 per minute, and the blood pressure 100 mm. Hg systolic and 65 mm. diastolic. Gastric lavage was repeated, and he was transferred to a ward for observation.

Vomiting continued throughout the first few days of hospitalization. At first the vomitus was blood-streaked, but it soon became clear. The stools were loose, some tinged with bright red blood, others colored dark brown. On the first two days following admission, urine was voided on several occasions, but on the third day a period of complete anuria supervened and lasted for five days. On the third day following admission the blood pressure rose to 150 mm. Hg systolic and 90 mm. diastolic.

Dimercaprol was not administered immediately because it was felt that treatment had been prompt and that very little of the ingested mercury had been absorbed. On the day after admission, however, a course of therapy was begun, dimercaprol being administered intramuscularly in dosage of 3 mg. per kilogram of body weight at intervals of four hours for eight doses. On the first day nothing was offered by mouth, and fluid requirements were met by administration of 0.9% saline and 5% dextrose in water intravenously. On the second and third days of hospitalization orally administered fluids were permitted.

Laboratory data were as follows: The hemogram on the second day of hospitalization disclosed a hemoglobin value of 10.0 gm. per 100 cc. and a white blood cell count of 21,950 per cubic millimeter, of which 80% were polymorphonuclear leucocytes. On the third day of hospitalization, the day on which oliguria began, the nonprotein nitrogen concentration of the serum was 135 mg. per 100 cc., the serum pH 7.30, chloride 88.4 mEq. per liter, and carbon dioxide content 13.3 mEq.. per liter.

When the period of anuria began, fluids were administered intravenously at a rate calculated to replace "insensible" losses of fluid and electrolyte.[12] Five hundred cubic centimeters of fluid, consisting of 50 cc. of isotonic saline and 450 cc. of 5% dextrose in water, was administered intravenously. On Feb. 22, 1952, the second day of anuria, the serum pH fell to 7.18, and sodium bicarbonate was administered intravenously. Calcium gluconate (10 cc. of 10% solution) was repeatedly given by vein to combat persistent hypocalcemia, and a cation exchange resin was given by mouth in doses of 20 gm. three times daily to aid in the elimination of potassium.[13] Diet was restricted to a flavored mixture of butter and sugar in order to provide a non-nitrogenous source of calories.[14]

Throughout the period of anuria, he remained reasonably cheerful and alert and complained only of hunger. A distaste for both diet and resin soon developed, although the butter-sugar mixture was accepted when suitably disguised and flavored. The blood pressure remained at an elevated level and several electrocardiographic tracings were compatible with the presence of hyperkalemia. Table 1 shows the concentrations of some of the solutes in the urine and plasma at various stages of his disease.

Renal Function During Recovery From Failure.—Of particular interest is the composition of the urine and plasma during recovery from acute renal failure. The values for concentration of total solutes, urea, sodium, chloride, potassium, and glucose are presented graphically in the

12. Butler, A. M., and Talbot, N. B.: Medical Progress: Parenteral-Fluid Therapy: Estimation of Losses Incident to Starvation and Dehydration with Acidosis or Alkalosis and Provision of Repair Therapy, New England J. Med. **231**:621, 1944.

13. Knowles, Harvey C., Jr., and Kaplan, S. A.: The Treatment of Hyperkalemia of Acute Renal Failure by the Use of Exchange Resins, to be published.

14. Bull, G. M.; Joekes, A. M., and Lowe, K. G.: Conservative Treatment of Anuric Uræmia, Lancet **2**:229, 1949.

TABLE 1.—*Composition of Serum and Urine During Recovery from the Acute Episode*

Date	Day Before or After Commencement of Urine Flow	Osmolarity		Sodium		Chloride		Urea		Bicarbonate		Glucose		Potassium		Calcium		Phosphorus		pH	Non-protein Nitrogen Plasma (Mg./100 Cc.)
		Urine (mOsm./L.)	Plasma	Urine (mMol./L.)	Plasma	Urine (mMol./L.)	Plasma	Urine (mMol./L.)	Plasma	Urine (mMol./L.)	Plasma	Urine (mMol./L.)	Plasma	Urine (mMol./L.)	Plasma	Urine (mEq./L.)	Plasma	Urine (mMol./L.)	Plasma	Plasma	
2/21 a. m.	—3	...	...	..	119	..	88	...	..	....	13.3	..	7.1	..	5.9	...	4.5	...	...	7.30	135
2/21 p. m.	—3	...	...	..	....	..	88	...	..	....	12.7	..	....	..	....	....	....	...	2.3	7.18	139
2/22 a. m.	—2	...	...	..	....	..	82	...	..	....	24.7	..	7.0	..	5.6	...	4.4	...	...	7.43	137
2/22 a. m.	—2	...	...	..	132	..	83	...	..	....	16.7	..	....	..	6.0	...	4.6	...	2.3	7.35	141
2/23 a. m.	—1	...	...	..	....	..	83	...	..	....	12.6	..	....	..	5.8	...	4.2	...	...	7.26	144
2/24 a. m.	1	280	312	128	128	72	83	40	40	....	16.8	..	7.1	13	5.8	2.5	4.0	2.3	...	7.27	171
2/24 p. m.	1	...	...	..	....	..	82	...	..	....	20.1	..	....	..	5.4	...	4.2	...	...	7.29	171
2/25	2	318	321	130	130	79	82	42	46	11.6	18.0	6	8.0	12	5.5	2.8	4.2	3.3	3.4	7.36	184
2/26	3	305	339	93	135	73	80	42	46	10.3	22.5	8	7.5	13	4.5	2.8	3.7	3.3	3.7	7.28	180
2/27	4	304	320	41	131	79	82	129	40	....	23.3	13	....	22	....	2.2	4.2	3.1	....	7.28	171
2/28	5	314	304	16	127	16	87	162	40	....	30.5	16	7.0	34	3.9	2.2	4.4	3.1	2.9	7.32	180
2/29 a. m.	6	325	312	16	134	16	92	181	30	....	28.7	23	....	58	4.2	1.8	4.7	3.1	....	7.25	140
2/29 p. m.	6	361	...	15	....	18	..	217	..	....	....	18	....	38	....	1.2	....	5.6	....	....	....
3/1 a. m.	7	333	324	14	141	17	96	211	24	....	28.2	15	....	34	4.9	1.3	5.1	6.3	....	7.44	106
3/1 p. m.	7	380	...	14	....	16	..	212	..	....	....	26	....	32	....	1.2	....	6.5	....	....	....
3/2 a. m.	8	376	...	37	....	39	..	174	..	....	....	25	....	29	....	1.9	....	3.5	....	....	....
3/2 p. m.	8	323	...	37	....	35	..	147	..	....	....	19	....	19	....	1.7	....	1.9	....	....	....
3/3 a. m.	9	370	310	34	140	38	103	197	10	....	25.5	19	....	37	5.3	1.8	....	5.7	....	7.36	52
3/3 p. m.	9	...	...	36	....	38	..	178	..	....	....	15	....	35	....	2.1	....	5.9	....	....	....
3/4 a. m.	10	386	319	60	145	60	106	169	13	....	22.6	13	....	32	5.1	....	4.8	7.6	....	7.35	60
3/4 p. m.	10	397	...	83	....	81	..	148	..	....	....	11	....	31	....	....	....	3.5	....	....	....
3/5 a. m.	11	426	...	53	....	65	..	195	..	....	....	10	....	43	....	....	....	11.4	....	....	....
3/5 p. m.	11	439	...	85	....	93	..	152	..	....	....	11	....	36	....	....	....	7.6	....	....	....
3/6 a. m.	12	451	325	61	150	73	108	178	9	....	25.8	6	....	52	....	....	....	16.3	....	7.31	34
3/6 p. m.	12	440	...	59	....	72	..	177	..	....	....	11	....	47	....	....	....	9.7	....	....	....
3/7 a. m.	13	445	...	76	....	79	..	146	..	....	....	5	....	63	....	....	....	8.5	....	....	....
3/7 p. m.	13	380	...	78	....	78	..	140	..	....	....	11	....	29	....	....	....	3.8	....	....	....
3/8	14	500	...	80	....	84	..	208	..	....	26.3	7	....	45	....	....	3.6	15.1	....	7.39	33
3/9	15	519	...	49	....	78	..	210	..	....	....	0.3	....	63	....	....	....	23.5	....	....	....
3/10	16	518	...	60	....	92	..	197	..	....	....	0.3	....	58	....	....	....	21.7	....	....	....
3/11	17	513	...	62	....	95	..	243	..	....	....	0.2	....	82	....	....	....	27.7	....	....	....
4/22	59	1053	320	160	146	207	109	293	9	....	....	..	....	87	3.6	....	....	....	....	....	....

Chart. Total osmolarity of the serum was calculated from the sum of the osmotic activity of its constituents.[15] Effective osmotic activity of the urine was determined directly by measurement of the depression of the freezing point. Sodium and potassium concentrations were determined by flame photometry, chloride by the method of Van Slyke,[16] calcium by a modification of the method of Sobel and Kaye,[17] pH of the serum by Hastings and Sendroy's[18] bicolor method,

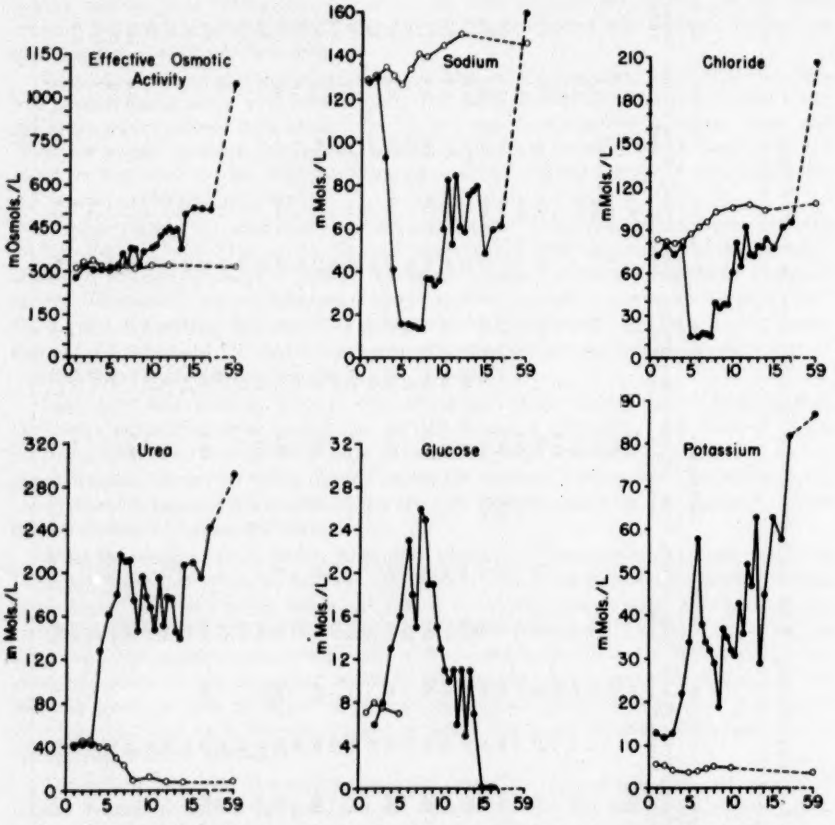

Fig. 1.—Composition of serum and urine during recovery from the acute episode. Open circle represents serum; black dot, urine.

15. Calculation of the osmotic activity of the plasma from the sum of the determined constituents as in this case fails to take into account two factors: first, that the coefficient of osmotic activity of the plasma is approximately 0.93 and, second, that not all the plasma constituents were determined. Fortunately, these two factors result in errors of almost equal magnitude in opposite directions and the value for plasma osmolarity as calculated is probably a close approximation of the true value.

16. Van Slyke, D. D.: Determination of Chlorides in Blood and Tissues, J. Biol. Chem. **58**:523, 1923.

17. Sobel, A. E., and Kaye, I. A.: Estimation of Submicroquantities of Calcium, Indust. & Engin. Chem., Anal. Ed. **12**:118, 1940.

18. Hastings, A. B., and Sendroy, J., Jr.: Studies of Acidosis: Colorimetric Determination of Blood pH at Body Temperature Without Buffer Standards, J. Biol. Chem. **61**:695, 1924.

carbon dioxide according to Van Slyke and Neill,[19] serum glucose by Nelson's[20] modification of the Somogyi method, urea by the method of Van Slyke and Kugel,[21] and phosphorus according to Fiske and Subbarrow.[22]

From the panel in the Chart depicting effective osmotic activity of the urine and plasma, it will be seen that urine and serum osmolarity were virtually equal during the first six days, at the end of which time concentrating ability of the kidneys was first evidenced by increasing urine osmolarity. Investigation of the processes of urine formation[23] has indicated that the first stage of modification of plasma is the process of filtration at the glomerulus, the filtered fluid having the solute composition of an ultrafiltrate of plasma. As fluid traverses the proximal tubule it undergoes further modification as solutes are added and abstracted but the effective osmotic activity remains equal to that of plasma. The distal tubule is concerned mainly with transfers of water, modifying the osmotic activity of fluid delivered from the proximal tubule under the influence of circulating antidiuretic hormone and the state of hydration of the body. The production of urine which is isotonic with plasma such as occurred in this case would therefore indicate the likelihood that the urine is either unmodified glomerular filtrate or proximal tubular fluid.[24]

The panels in the Chart referring to the concentrations of the individual solutes provide evidence which has a bearing upon the segment of the nephron which was functionally active at the time the urine entered the collecting systems. On the first two days of reestablishment of urine flow, the concentrations of urea, sodium, chloride, and glucose were almost identical in serum and urine. It seems reasonable to infer, therefore, that the urine formed on the first two days was practically unmodified glomerular filtrate. Over the next four days effective osmotic activity of the urine remained equal to that of serum, but within the ceiling of a constant osmotic activity, concentrations of the various solutes began to vary. Sodium concentration fell from 130 to 93 mEq. per liter on the third day, and on the next day as sodium concentration continued to fall precipitously the concentration of urea began to rise. The composition of the urine on the third to sixth days is consistent with the hypothesis that the proximal tubule was preferentially beginning to reabsorb certain solutes while maintaining constant the total tonicity. The urine formed on these days is reminiscent of fluid obtained by micropuncture of the proximal tubules of mammalian kidneys.[23] It is of interest to note the changes in composition of the serum as proximal tubule function returned. The concentration of sodium and chloride began to rise from the low levels seen on the first two days to more nearly normal levels, while the serum urea concentration gradually declined.

The presence of glucose in the urine during recovery is of interest. On the first three days of recovery of function concentration of glucose in the urine did not deviate appreciably from that in the plasma. As recovery of function of the proximal tubules occurred, the concentration of glucose in the urine rose appreciably. The tubular handling of glucose during recovery thus resembled that of urea, and it must be deduced that there was considerable impairment of glucose reabsorption. The abstraction of isotonic solution containing little glucose would leave behind proximal tubular fluid containing glucose in high concentrations, such as was found

19. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523, 1924.

20. Nelson, N.: Photometric Adaptation of Somogyi Method for the Determination of Glucose, J. Biol. Chem. **153**:375, 1944.

21. Van Slyke, D. D., and Kugel, V. H.: Improvements in Manometric Micro-Kjeldahl and Blood Urea Methods, J. Biol. Chem. **102**:489, 1933.

22. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

23. Walker, A. M.; Bott, P. A.; Oliver, J., and MacDowell, M. C.: Collection and Analysis of Fluid from Single Nephrons of the Mammalian Kidney, Am. J. Physiol. **134**:580, 1941.

24. Because of the nature of the renal filtering apparatus which retains the plasma proteins, the concentration of electrolyte in glomerular filtrate differs from that in the plasma and may be calculated by applying the Donnan factor. With average plasma protein concentration the Donnan factor introduces a change of 6% for sodium and potassium and 3% for chloride. Greene, C. H.; Bollman, J. L.; Keith, N. M., and Wakefield, E. G.: The Distribution of Electrolytes Between Serum and Transudates, J. Biol. Chem. **91**:203, 1931.

by Walker and associates in the proximal tubular fluid of animals which had received phlorhizin.[23] It is noteworthy that the maximal urine: plasma ratio for glucose in proximal tubular urine found by these investigators in phlorhizinized animals was 3 and that this was the maximal urine: plasma ratio observed in the case reported here.

The mechanism underlying the interference with reabsorption of glucose in cases of poisoning with mercuric chloride is obscure. Simonds and Hepler [2] found glucosuria in about one-fourth of their series of dogs poisoned with mercuric chloride, but noted that there was no correlation between the degree of impairment of alkaline phosphatase activity in the blood or kidneys and the presence of glucose in the urine. Thus it appears unlikely that glucosuria is a consequence of impairment of phosphatase activity. Since the mechanism of enzymatic transfer of glucose by the kidneys is still obscure, further speculation on the factors underlying glucosuria in cases of poisoning with mercuric chloride is not warranted at this juncture.

With the return of distal tubular function on the 7th day, urine osmolarity gradually rose until, on the 14th day, values exceeding 500 mOsm. per liter were encountered. However, on the 17th day, the day of discharge, concentrating power was still poor. Despite a period of water deprivation of 14 hours, the patient was unable to produce a concentration greater than 513 mOsm. per liter. Under similar conditions children with normal renal function produce urine with an effective osmotic activity greater than 1,000 mOsm. per liter.[25]

Six weeks after the period of anuria, studies of specific renal functions were made. At that time he was able to concentrate to 1,053 mOsm. per liter following a 14-hour period of water

TABLE 2.—*Renal Function on the Fifty-Ninth Day After Recommencement of Urine Flow*

	Patient	Normal Controls *	
		Mean	S. E.
Urine osmotic activity after 16 hr. of water deprivation	1,053	1,104	32
Glomerular filtration rate †	75	83.6	2.1
Renal plasma flow †	362	596	16
Urea clearance †	49	63.3	1.8

* Data from 16 patients.
† Average of 3 periods.

deprivation and responded to loading with hypertonic mannitol by exhibiting a normal flow-load relationship [26] and normal urine electrolyte concentrations. That recovery of renal function was not yet complete was evidenced by comparison of the rates of renal blood flow, filtration, and urea clearance with corresponding values for normal persons (Table 2).[26]

COMMENT

In the normal kidney, in addition to modifying glomerular filtrate, the tubules serve as channels through which fluid is transported to the collecting systems. In recovery from acute failure the first tubular function to return in the case reported here appeared to be the mechanical ability to conduct fluid to the collecting system. If filtration were proceeding, even at a reduced rate, flow of urine would begin again when this conducting ability had returned, and the first specimens of urine voided would have the same composition as glomerular filtrate.[27]

25. Rapoport, S.; Brodsky, W. A.; West, C. D., and Mackler, B.: Urinary Flow and Excretion of Solutes During Osmotic Diuresis in Hydropenic Man, Am. J. Physiol. **156**:433, 1949.

26. Brodsky, W. A.; Rapoport, S.; Graubarth, H. N., and Levkoff, A. H.: Osmotic Diuresis as a Measurement of Renal Function in Man, J. Applied Physiol. **5**:62, 1952.

27. It must be concluded that very few glomeruli were patent or that very few nephrons were sufficiently intact to conduct fluid to the collecting systems. Since the rate of glomerular filtration approximates 180 liters per day for an adult (and somewhat less for children), the loss of unmodified glomerular filtrate from all glomeruli would result in enormous losses of fluid from the body. It is fortunate indeed that recovery proceeds in a manner which obviates this hazard.

Under conditions of health, solutes are abstracted in the proximal tubule in a fluid, the total tonicity of which is equivalent to that of an ultrafiltrate of plasma.[23] The fluid remaining behind in the tubule must therefore be of the same tonicity. Some solutes, such as sodium and chloride, are preferentially removed, leaving behind others, such as urea and creatinine, in higher concentration. As recovery progressed in the case reported here, proximal tubular function returned within a few days, but it was almost eight weeks before distal tubular function (as evidenced by concentrating ability) returned completely. If the time taken for a segment of the nephron to recover can be taken as an index of the severity of its involvement, it may be argued that the distal nephron was more severely involved than was the proximal. On the other hand, it may well be that the proximal portions are affected more severely but repair more easily and quickly. Morphological evidence would seem to favor the latter hypothesis, since the studies of Oliver and associates have shown that following ingestion of mercury damage is more widespread proximally than distally [3] and also that regeneration of new proximal epithelium begins promptly, mitotic figures being visible within a few hours.[28] On the other hand, if any distal lesions are present, they are of the tubulorhectic type and, since there is disruption of the basement membrane, healing may never occur in these sites. Another possibility to be considered is that distal tubular insufficiency, which was so prominent a feature in the case reported here, may not be detectable by the techniques available to the morphologist. Assuming that tubulorhexis was responsible for distal tubular insufficiency, the disruptive lesions would have been widespread and must have involved the majority of the nephrons. Under these circumstances, however, the possibility of ultimate recovery such as occurred in this case must be extremely doubtful. Until further information is available on the assessment of distal tubular insufficiency by morphological and functional techniques, judgment on this apparent discrepancy between anatomy and physiology must be suspended. Studies which may yield information bearing on this problem are now in progress.

Failure of the concentration of urea in the blood to return to normal when flow of urine begins again is explained by the composition of the urine and plasma in the initial stages of diuresis. The amount of plasma cleared of urea depends on the rate of excretion of urea and the plasma concentration and is calculated from the expression UV/P where U and P represent the concentrations of urea in urine and plasma respectively and V the rate of flow of urine per unit of time. Because the U/P ratio of urea was unity in the first three days after return of renal function, urea clearance was equal to urine flow ($U/P = 1$, therefore $UV/P = V$). For urea clearance to rise to normal levels with a urine flow of 3 liters per day per 1.73 square meters of body surface area (2.3 cc. per minute) the U/P ratio must rise to about 20. This level was not reached until eight days after recommencement of flow of urine.

From the first day of return of urine flow the concentration of potassium in the urine was nearly twice as great as in the plasma. This discrepancy is the only major objection to the hypothesis that glomerular filtrate was being conducted unchanged to the collecting systems on the first and second days on which urine was being formed. It may be argued that the first function of the proximal

28. Oliver, J.: Personal communication to the author.

tubule to return is that which is concerned with the elimination of potassium and that proximal regeneration had already reached the stage where this function could be performed when urine flow first commenced.

Fluid replacement therapy during the initial stages of diuresis will be guided by a knowledge of the composition of the fluid being lost from the body. This fluid may be identical in composition with an ultrafiltrate of plasma (virtually extracellular fluid) and it would thus appear rational to replace the fluids either with isotonic saline or solutions similar in composition to extracellular fluid, such as Ringer's solution. Since the kidneys possess little or no ability to excrete or retain solutes selectively, such replacement should be administered by the intravenous route; in this way the bowel wall will not modify the administered solution. With return of renal function the difficulties of replacement therapy diminish, and, provided enough water and electrolyte are administered, renal function will maintain constant the composition of the body fluids.

SUMMARY AND CONCLUSIONS

Evidence is presented that in an ischemuric episode following ingestion of mercuric chloride there was return of function, first of the glomeruli, then of the proximal portions of the nephron, and finally of the distal segments. An analysis is made of observations of others which indicates that the pattern of recovery observed in this case correlates well with current knowledge of the structural and functional impairment of the nephrons which may occur in acute renal failure.

Dr. Harvey C. Knowles Jr. and Dr. M. R. Stewart assisted with this study.

USE OF SULFONAMIDES AND PENICILLIN TO PREVENT RECURRENCE OF RHEUMATIC FEVER

A Twelve-Year Study

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IN THE YEAR 1939, Thomas and France [1] and Coburn and Moore [2] reported their use of sulfanilamide in preventing the recurrence of rheumatic fever. Since then, many other reports have confirmed their results and have shown that other sulfonamides are similarly effective. In 1940, at the Children's Heart Hospital, we began to administer sulfanilamide to a small number of patients. During the following decade, we continued this administration, using various sulfonamides and each year increasing the number of children receiving the drug. Then, following Massell's [3] report, we replaced the sulfonamides with orally administered penicillin for two years. The results of these studies concur with those already published and are therefore not unusual. However, these results represent 12 years of administration and observation. Moreover, they afford an indirect comparison of the efficacy and toxicity of the sulfonamides versus orally administered penicillin. For these reasons, they may be of special interest.

MATERIAL AND METHOD

The Children's Heart Hospital has a capacity of 60, an average occupancy of 98.5%. Its patients, equally divided between the sexes, range in age from 3 to 15 years. Of the 661 children who were admitted to the hospital between Sept. 1, 1940, and Sept. 1, 1950, 638 had rheumatic fever, with or without rheumatic heart disease.

Selection of Patients.—During the first four years of the study, only those patients who were free of all evidence of rheumatic activity were given sulfanilamide. As experience was gained with the drug and as other sulfonamides became available, this rigid selection was somewhat modified to include children in whom activity was still present, though not fulminant. This criterion was further relaxed to include patients with moderately severe carditis during the two years in which orally administered penicillin replaced the sulfonamdes as a prophylactic agent.

At first, from September, 1940, to September, 1942, an equal number of patients and controls was observed. From then on, however, no controls were used. Instead, we tried to place all rheumatic-susceptible patients on a sulfonamide (or later, penicillin) regimen as soon as it was found advisable. As one might expect, however, we were not completely successful, for some patients had to be excluded because their histories showed untoward reactions to sulfonamides.

1. Thomas, C. B., and France, R.: A Preliminary Report of the Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, Bull. Johns Hopkins Hosp. **64**:67-77 (Jan.) 1939.

2. Coburn, A. F., and Moore, L. V.: The Prophylactic Use of Sulfanilamide in Streptococcal Respiratory Infections, with Especial Reference to Rheumatic Fever, J. Clin. Invest. **18**: 147-155 (Jan.) 1939.

3. Massell, B. F.; Dow, J. W., and Jones, T. D.: Orally Administered Penicillin in Patients with Rheumatic Fever, J. A. M. A. **138**:1030-1036 (Dec. 4) 1948.

Others, although initially included in the study, remained in the hospital for less than three months after either the sulfonamide or the penicillin was first administered. No observations of significance were contributed on these, and they are therefore not included in this report.

The Sulfonamide Regimen.—During the first three years of the study, the treatment was confined to the period between Sept. 1 to June 1; during the next seven years, it was continuous throughout the year. In this first three years, full therapeutic doses of sulfanilamide were given, ranging from 3 to 6 gm. daily in divided doses, sufficient to maintain a serum level of 4 to 5 mg. per 100 cc. From 1943 to 1945, this dose was gradually reduced to 0.5 gm. daily for children weighing less than 75 lb. and to 1 gm. daily for children weighing 75 lb. or more. From 1945 to 1950, this lowered dose was used. As for the selection of sulfonamide, sulfanilamide was used from 1940 through 1947, and sulfamerazine, or equal parts of sulfamerazine and sulfadiazine, was used from 1943 to 1950. The number of children to whom each of these three forms was given may be found in Table 1.

As has been mentioned, we replaced, for reasons that will be presented below, the sulfonamides with orally administered penicillin from May, 1950, to July 1, 1952. During that period, we treated 102 children, representing more than 90% of the hospital census. Each child, regardless of age, was given 100,000 units twice a day of crystalline penicillin G in a palatable liquid form.[4] No special effort was made to give the penicillin on a fasting stomach. As a matter of fact, the first dose was given one-half hour or less before breakfast, and the second dose was given (inadvertently, at first), with the afternoon fruit juice.

TABLE 1.—*Efficacy and Toxicity of Sulfonamides and of Orally Administered Penicillin in the Prevention of Recurrences of Rheumatic Fever*

Type of Sulfonamide	No. Patients Started	Toxic Reactions	No. Patients Treated for 3 Mo. or More	No. Patient Yr.	Recurrences of Rheumatic Fever
Sulfanilamide	179	25	154	72	0
Sulfamerazine	197	5	192	105	1
Sulfamerazine and sulfadiazine (equal parts)	125	4	121	75	1
Totals	501	34	467	252	2
Penicillin	102	0	102	55	0
Totals	603	34	569	307	2

Laboratory Studies.—During the decade of sulfonamide prophylaxis, hemoglobin concentrations, white blood cell counts, erythrocyte sedimentation rates, sulfonamide levels, and urinalyses were recorded three times weekly during the first month that the child was given the drug, then weekly for two months, then every three weeks during the remainder of the hospital stay. After 1944, serum levels were no longer determined. The laboratory studies of the children to whom penicillin was administered included a complete blood cell count and urinalysis three times a week for two weeks, once a week for four weeks, then once every three weeks. From 1940 to 1942, electrocardiograms were done monthly; from 1943 to 1952, they were done when indicated.

Clinical Observations.—Each patient was weighed weekly; each patient's temperature, pulse, and respiratory rate were recorded twice daily. A physician examined each patient at least once a week and checked each chart at least three times a week. Additional examinations were made promptly whenever changes in the patient's course were reported.

RESULTS

As Table 1 shows, we treated 467 hospitalized children with sulfonamides for periods ranging from three months to two years. Of these, only two (0.4%) experienced recurrences of rheumatic fever. Table 1 also shows that of the 102 patients who received crystalline penicillin G from May 1, 1950, to July 1, 1952,

4. The penicillin preparation used throughout this study was Eskacillin 100, trademark of product of Smith, Kline & French Laboratories.

none experienced recurrence. Thus it would appear that orally administered penicillin is at least as effective as the sulfonamides as a prophylactic agent.

Although there was no recurrence of rheumatic fever among the children who were given penicillin, there were three outbreaks of upper respiratory tract infections that superficially resembled the prodrome of rheumatic fever. These outbreaks occurred in November, 1951, and in January and March, 1952, and each time affected more than half of the population of the hospital. In November, 1951, for example, nose and throat cultures from the 60 children in the hospital at that time revealed penicillin-resistant hemolytic Staphylococcus aureus in 46. Of these 46, 37 had, or had had, an upper respiratory tract infection with acute pharyngitis, fever and leucocytosis.

We emphasize that the low incidence of recurrence described above applies to patients who were hospitalized during the period of administration and observation. It may well be asked, What was the incidence of recurrence after discharge from the

TABLE 2.—*Reactions to the Sulfonamides: Type, Number of Patients, and Time of Appearance*

Drug	Type of Reaction	No. Patients	No. of Days Between First Dose and Appearance of Reaction		
			Minimum	Maximum	Average
Sulfanilamide	Skin	7	3	60	21
	Vomiting	8	1	14	5
	Hematologic	7	5	56	30
	Albuminuria	2	52	128	..
	Epitaxis	1	5	..	..
	Paroxysmal tachycardia	1	2	..	..
Sulfamerazine	Skin	2	2	60	..
	Weight loss	2	..	..	..
	Hematologic	1	60	..	..
Sulfamerazine and sulfadiazine 1:1	Skin	1	2	..	..
	Vomiting	1	30	..	..
	Albuminuria	2	21	80	..

hospital? From August, 1945, to Sept. 1, 1950, the parents or guardians of each of the children who had been taking sulfonamides were given a two-weeks' supply of sulfonamide at the time of discharge and were advised to consult, within 10 days, either their family physician or a clinic. Fifteen of these children were later readmitted to Children's Heart Hospital with rheumatic recurrence. All of these 15 had stopped taking the sulfonamide before the onset of recurrence. As a matter of fact, they had stopped taking it for periods of three months to two years (average, seven months) before the recurrence. Little can be said about the possibility that some of our patients, perhaps even those who faithfully followed the sulfonamide regimen after discharge, might have experienced recurrences that did not come to our attention. However, this much can be said: Since 1945, we have been apprised by physicians in this area that 10 recurrences of rheumatic activity have appeared among children who had been included in this study. Further investigation of each recurrence revealed, however, that the children had discontinued sulfonamide therapy more than six weeks before the recurrence.

As for recurrences after discharge among those who were included in the penicillin study, all of the parents or guardians were given a two-weeks' supply of the

penicillin preparation for oral administration that had been used throughout the two-year study. Ten of these patients have been followed closely; since August, 1951, none has experienced recurrence. Another patient, who had been hospitalized in June, 1950, with rheumatic fever and rheumatic carditis, was discharged on Aug. 10, 1951, completely free of activity. He was readmitted on Oct. 22, 1951, with a fulminating recurrence of rheumatic fever. When questioned, his parents revealed that they had failed to give him penicillin once the two-weeks' supply had been exhausted.

Table 1 also shows the number of patients who while on sulfonamide therapy experienced reactions severe enough to force discontinuance of therapy. Table 2, on the other hand, defines the type of reactions experienced, as well as the time at which they appeared following the institution of sulfonamide therapy. As has been mentioned, in the first three years of the study full therapeutic doses of sulfanilamide were given. At that time, the high incidence of reactions was assumed to be in part due to the size of these doses. However, this assumption was later proved to be wrong, for even when the dose of sulfanilamide was reduced to 1 gm. or to 0.5 gm., the incidence of toxicity remained approximately the same. In all patients, the toxic signs and symptoms disappeared when the sulfonamide was discontinued.

Of special interest was the fact that in all of the 55 patient years that the penicillin part of the study represented there were no untoward reactions to the crystalline penicillin G preparation. Moreover, the palatability of the preparation made its administration to the children uncommonly easy.

COMMENT

In evaluating the efficacy of any prophylactic measure, one must depend upon comparisons with the efficacy of other measures or of no measures at all. Thus, the incidence of recurrence of rheumatic fever in those patients admitted to the Children's Heart Hospital prior to the institution of the sulfonamide regimen should provide a useful background. From Sept. 1, 1938, to Sept. 1, 1939, there were 20 acute recurrences (24%) among 82 patients. From Sept. 1, 1939, to Sept. 1, 1940, there were 18 acute recurrences (25%) among 72 patients. During the two periods from Sept. 1, 1940, to June 1, 1941, and from Sept. 1, 1941, to June 1, 1942, when, as has been mentioned, an equal number of patients and controls were observed, another comparison was possible. In these periods, of the 44 patients who could tolerate sulfanilamide (8 could not), none experienced recurrence of rheumatic fever. Of the 44 controls, none of whom received sulfanilamide, 9 (20%) experienced recurrence. This comparison is the most valid that we can make since it is, as far as can be determined, a comparison of only one variable—the use or nonuse of sulfanilamide.

The observations made during the next 10 years of the study were, as we have said, made on the basis of uncontrolled studies with sulfonamides and orally administered penicillin. These observations, however, seem none the less significant since there were but two recurrences in the large group given sulfonamides and none at all in the group given penicillin—an incidence far below what we and others have come to expect when no prophylactic steps are taken. Of course, those few observations that we were able to make after the children were discharged from the hospital are bound to be merely provocative and not in any sense complete.

One thing apparent in our results is the rather frequent appearance of untoward reactions to the sulfonamides. These reactions, especially frequent with sulfanilamide, less so with other forms, removed almost 7% of the patients from the study, and, more important, deprived them of the prophylactic effects of the regimen. As disconcerting as the reactions themselves was the fact that they often made their appearance long after the institution of the regimen.

It was these reactions, coupled with the opinion of Massell,[8] that suggested to us the substitution of orally administered penicillin for the sulfonamides. As a result, we conclude that the continuous use of sulfonamides does indeed prevent the recurrence of rheumatic activity, but that oral penicillin, which appears to be equally effective, has an important advantage—it does not appear to cause toxic reactions.

SUMMARY

Of 501 children considered likely subjects for a study of the prevention of recurrences of rheumatic fever, 467 were given one of various forms of sulfonamides for from three months to two years over a 10-year period. Only two of these experienced recurrences, as compared to 9 recurrences in a group of 44 controls, or as compared to 38 recurrences in a group of 154 patients observed in a two-year period prior to the decade of this study. The other 34 children experienced untoward reactions to the sulfonamides.

In the last two years of the 12-year study, orally administered penicillin was substituted for the sulfonamides in the treatment of 102 children. None of this group had a recurrence of rheumatic activity; none had toxic reactions of any kind.

ERYTHEMA NODOSUM

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ERYTHEMA nodosum has been recognized as a disease entity for more than 100 years. It was first reported by Buillard in 1840, in his classical treatise on acute rheumatic fever. His concept of the disease was generally accepted for a number of years.

The French workers, notably Poncet (1886) and others, as well as Uffeleman (1876), of Germany, were the first to suggest the tuberculous origin of erythema nodosum because they had observed the association of the disease with tuberculosis. Very soon Scandinavian workers, Ernberg in 1933 [1] and Wallgren in 1931 and 1938,[2] published reports suggesting tuberculous origin in large series of cases. Their work was significant, as they were dealing with a childhood age group in which the incidence of tuberculin sensitivity is normally much lower than in the adult group. They concluded that the cutaneous eruption occurred early in the disease at the height of the tuberculin sensitivity and represented the change-over from the pre-allergic to the allergic phase.

The most commonly associated infection in European countries is tuberculosis, and Wallgren (1930) has shown that the appearance of the rash coincided with the development of tuberculin sensitivity in about 95% of their cases, but he admits that in 5% there was a persistent negative reaction and the disease was, therefore, of nontuberculous origin.

Considerable interest has been attached to the number of cases of erythema nodosum in which the patients consistently show negative tests to doses up to 1 mg. of tuberculin. The Scandinavian authors (Wallgren [2] 5%, Ostevdt 16.9%, and Ernberg [1] 11.9% of 454 cases, of Sweden, and Rollof [3] 19 out of 77 cases, and Ustevdt 15%) report a much lower incidence of nontuberculous cases than the American writers (Spink,[4] of Boston, 47%, Favour and Sosman,[5] of Boston,

1. Ernberg, H.: Erythema Nodosum and Tuberculosis, Am. J. Dis. Child. **46**:1297, 1933.

2. Wallgren, A.: Tubercle Bacilli in Children with Erythema Nodosum, Am. J. Dis. Child. **41**:816, 1931; Erythema Nodosum and Pulmonary Tuberculosis, Lancet **1**:359, 1938; Rheumatic Erythema Nodosum, Am. J. Dis. Child. **55**:897, 1938.

3. Rollof, S. I.: The Occurrence of Erythema Nodosum in Children with Primary Tuberculosis, Treated with Sulphathiazole, Acta paediat. **32**:690, 1945; Erythema Nodosum in Association with Sulphathiazole in Children, Acta tuberc. scandinav., 1950, Supp. 24, p. 1.

4. Spink, W. W.: Pathogenesis of Erythema Nodosum, Arch. Int. Med. **59**:65, 1937.

5. Favour, C. B., and Sosman, M. C.: Erythema Nodosum, Arch. Int. Med. **80**:435, 1947.

47.5%). Ernberg and Gabinus[6] in the first half of 1937 reported 20 cases of erythema nodosum which occurred in close succession, in each of which tuberculin tests were repeatedly negative, and they concluded that pharyngeal infection preceded the eruption in the majority of cases.

Smith,[7] of California, in 1940 reported a series of cases of erythema nodosum in conjunction with coccidioidomycosis. In five of the cases, the sensitivity test was negative in the initial phase of the disease and became positive after the appearance of the eruption.

The 105 cases of erythema nodosum included in this series were observed at The Hospital for Sick Children in Toronto during the past 27 years. All patients were admitted to the hospital, and no cases are included in which the patients were treated only in the outpatient department.

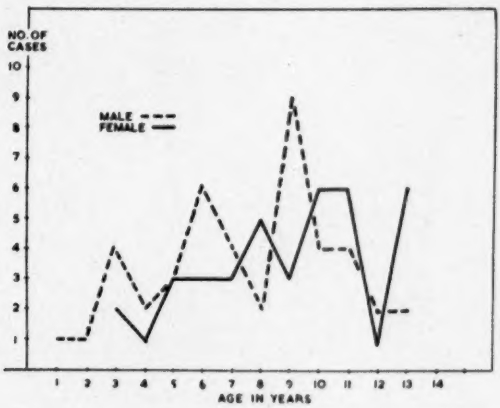

Chart 1.—Age and sex incidence of erythema nodosum.

CLINICAL OBSERVATIONS

Age Incidence.—In all but one of the total number of cases, the patients were under 14 years of age, the youngest being 15 months of age. The patients were over 5 years of age in 87.6% of the cases, the incidence being almost equal in the 5- to 10-year and 10- to 14-year period (Chart 1). In both periods, there was a slight predominance of girls, but not great enough to be statistically significant. So that, before the age of puberty, the sex incidence is about equal, but after puberty, female sex hormones may be a contributing factor. Spink,[4] of Boston, noted 111 women and 22 men in 133 cases of erythema nodosum in adults.

Age of Onset.—The age of onset varied from 15 months to 14 years of age, with the disease developing in children between 5 and 14 years of age in 87.6% of the cases.

6. Ernberg, H., and Gabinus, O.: Close Succession of Cases of Erythema Nodosum of Non-tuberculosis Pathogenesis, Am. J. Dis. Child. **57**:1012, 1939.

7. Smith, C. E.: Epidemiology of Acute Coccidioidomycosis with Erythema Nodosum, Am. J. Pub. Health **30**:600, 1940.

Seasonal Incidence.—The greatest number of cases occurred in the late fall, early winter, and spring, the incidence reaching a low level in summer and early fall (Chart 2). These findings agree with Favour and Sosman,[5] of Boston, although Spink,[4] also working in Boston, reports a peak in the early spring months, which corresponds with the peak incidence of streptococcal infection in the New England States.

Family History.—In only a few cases was there a positive family history of either tuberculosis or rheumatic fever. In two families, there was a history of two or more cases of erythema nodosum among the brothers and sisters. In one, the child herself had had similar illnesses, lasting approximately one month, during each of the four preceding winters. On admission to hospital, the intracutaneous tuberculin test was negative, but it became positive two weeks later. There was no known

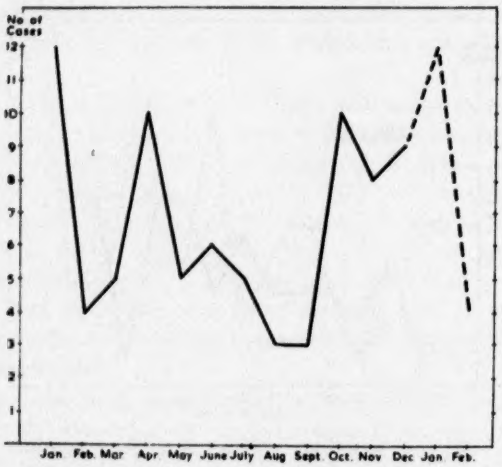

Chart 2.—Seasonal incidence of erythema nodosum.

exposure to tuberculosis. Seven siblings in her family are reported to have had similar skin lesions in childhood.

The other family is interesting in that there were three children in the home with this particular skin eruption. Erythema nodosum developed in the 13-year-old daughter five days after the onset of sulfadiazine therapy for acute tonsillitis. Three weeks after the onset of her illness, her 9-year-old brother had a sore throat and typical erythema nodosum. He had had a similar episode two years previously and had not had sulfadiazine on each occasion. A sore throat and typical erythema nodosum also developed in the 11-year-old boy one week after that in his brother, and he also had not had sulfadiazine. The 9-year-old boy has since had a third recurrence of erythema nodosum associated with a severe upper respiratory infection with which he was acutely ill. These three children continue to show negative reactions to 1 mg. of old tuberculin.

In 4 cases, there was a family history of rheumatic fever, and in 13 cases, there was a history of tuberculosis, although 2 of these were doubtful. Three of these

patients were contacts of patients with positive sputum, and each of these had x-ray evidence of mediastinal or pulmonary lesions.

Past History.—A history of repeated and chronic upper respiratory infection was common, and acute upper respiratory infection preceded the appearance of the erythema nodosum in 47 cases (52.8%). On admission to the hospital, approximately 50% of the patients had diseased tonsils, which may be a significant finding in view of the frequent relationship of this syndrome to hemolytic Streptococcus infections. The interval between the occurrence of the respiratory infection and the appearance of the erythema nodosum varied from 1 day to 6 weeks, the average being 10 days.

Physical Examination.—All but seven of the children in this series were well nourished and well developed. The one constant finding, in each case, was the cutaneous skin eruption, which occurred usually over the tibial surfaces of the legs; less frequently over the ulnar surfaces of the arms, and occasionally on the soles, the thighs, the buttocks, and the shoulders. In several patients, the rash was directly related to trauma; in two instances the patients were admitted with a diagnosis of acute osteomyelitis.

Typically, the eruption first appeared as a series of firm raised purplish-red tender nodules about 1 to 3 cm. in diameter. With the development of erythema and edema, the nodules became larger, frequently coalesced, became bluish in appearance, and often were fluctuant, although none in the series suppurated. About one week after the onset, the nodules began to regress, and in another week they became smaller and gradually disappeared, leaving a discoloration of the skin as well as fine scaliness and thickening.

The test for sedimentation rate was not done on all patients, but the rate was consistently elevated in all cases in which it was reported. It varied from 20 to 40 mm. in one hour, slowly falling to normal over a period of four to six weeks after onset of the cutaneous eruption.

Tuberculin-Positive Group (55 Cases).—All tuberculin tests were done by the intracutaneous method, using a dose of from 1/20 mg. up to 1 mg. of old tuberculin. No patch tests were used.

The patients in 55 cases in this series had positive tuberculin reactions and fall into the group of tuberculous erythema nodosum. Forty-four of these (80%) showed positive reactions on admission to the hospital; in eight the reactions became positive in from 1 to 10 weeks after admission, and in three they became positive in from 4 to 6 months after admission.

Of the 44 patients admitted with positive skin tests, 13 had a known exposure to tuberculosis, 5 of these had had a close contact for periods up to six months, and 2 of these contacts had positive sputum. Another of these 13 children had a known close contact nine months before the onset of the erythema nodosum, and at the time of onset had well-advanced bilateral pulmonary disease. Another child had a known contact with a patient with positive sputum 10 years before admission and a positive reaction developed at that time, but at the onset of the erythema nodosum, there was no x-ray evidence of primary tuberculosis. Eight of these patients with known exposure to tuberculosis had x-ray evidence of mediastinal tuberculosis, and three

had pulmonary disease, one with an associated pleural effusion. Details of the extent of the contact of the remaining six patients are not available.

In 11 cases, tuberculin conversion occurred, and in eight of these patients, it occurred within 2 to 10 weeks after the onset of symptoms, which interval corresponds to the accepted incubation period of tuberculosis. In three cases, conversion occurred in 4 to 6 months after the onset of the erythema nodosum. There was no history of contact with tuberculosis in any of the 11 cases, but in four there was definite x-ray evidence of mediastinal or pulmonary disease.

In one child with a positive tuberculin reaction on admission, the erythema nodosum occurred one month after cessation of treatment with old tuberculin for tuberculous cervical adenitis.

In another child admitted to the hospital with mastoiditis and streptococcal meningitis, erythema nodosum developed six weeks after onset of the illness, and the tuberculin test became positive seven weeks after onset of the illness. One wonders if this represents a true tuberculin conversion or a depression of tuberculin sensitivity during the meningitis, with the erythema nodosum appearing with the rise in allergy after the meningitis was controlled. We do know that a depression of allergy occurs during measles.

Of our 55 patients, 19 showed x-ray evidence of mediastinal tuberculosis with or without streaking to the periphery; 7 had mediastinal tuberculosis with a primary calcification in the periphery (two of these had an associated pleural effusion), and 7 had pulmonary tuberculosis, 3 of these with bilateral disease and one with an associated pleural effusion. Of these, 13 had had a definite contact. In 22 cases the patients had no x-ray evidence of disease, but most of these occurred during the first 10 years of the study, for which no x-rays are available for assessment.

In 80% of the cases in which the patients had positive reactions, they were positive on admission to the hospital, and in 60% of these there was x-ray evidence of tuberculous disease. For the earlier cases in the study, no x-ray records were available, so that this figure might conceivably be higher. While this is not convincing proof of the tuberculous origin in these cases, it is very suggestive and in agreement with figures from other centers.

The positive tuberculin reaction is the best guide to a diagnosis of tuberculous origin of erythema nodosum.

Tuberculin-Negative Group (50 Cases).—Fifty cases, or 47.6%, in our series occurred in children who had negative tuberculin tests on admission to the hospital, and they remained negative on subsequent testing, in dilutions up to 1 mg. of old tuberculin. These children were kept under observation and repeatedly tested up to six months after the occurrence of their erythema nodosum.

Upper respiratory infections and tonsillitis are the most common infections preceding erythema nodosum in the tuberculin-negative group and occurred in 32 cases in this series. This is perfectly reasonable in that upper respiratory infections are the most common infections children encounter and the most frequently repeated.

In one family, previously mentioned, there were three children in the home with this particular skin eruption. Erythema nodosum developed in the 13-year-old daughter five days after the beginning of sulfadiazine therapy for acute tonsillitis. Three weeks later a sore throat and a typical erythema nodosum developed in her 9-year-old brother. He had had a similar episode two years previously and had not

had sulfadiazine on either occasion. A sore throat and a typical erythema nodosum also developed in the 11-year-old boy one week after that in his brother, and he also had not had sulfadiazine. The 9-year-old boy has recently had a third recurrence of erythema nodosum with an acute pharyngitis.

Rheumatic fever has, for the last 50 years, been considered a cause of erythema nodosum, but there is no evidence to support this view. Polyarthritis, migratory pains, etc., do occur in association with erythema nodosum, especially in adults, but it is now clear that these pains are by no means characteristic and occur as frequently in tuberculin-positive as in tuberculin-negative individuals with erythema nodosum. There is no doubt that erythema nodosum can occur in association with rheumatic fever, and it is likely that the streptococcal infection is the exciting factor in a predisposed individual. In our series, there was not one case of rheumatic fever ushered in by the occurrence of erythema nodosum, although in two cases the migratory pains and polyarthritis persisted and responded to salicylate therapy.

In this group with negative tuberculin tests, 27 patients, or 54%, had diseased tonsils and adenoids, and in the tuberculin-positive group, 19, or 33%, had diseased tonsils and adenoids. In the whole series, about 24 patients had positive throat cultures for hemolytic streptococci, but as less than half of the patients had any culture taken this figure is of no significance.

Chemical Erythema Nodosum.—Twelve cases in this series might be classified as erythema nodosum due to sulfathiazole and occurred in association with tonsillitis, cervical adenitis, mastoiditis, osteomyelitis, streptococcal meningitis, and pneumonia. The erythematous rash appeared in from one to six weeks after the onset of the infection and on the average about eight days after the commencement of chemotherapy. No absolute diagnostic difference was observed between the lesions associated with sulfathiazole and the lesions of the spontaneous eruption. In the drug eruption, however, the nodules were smaller, more circumscribed, much less tender, and appeared within a few days after starting use of sulfathiazole therapy. The lesions cleared up rapidly on stopping use of the drug therapy without passing through the color phases usually seen in the spontaneous type of erythema nodosum.

It appears that sulfathiazole and related drugs can provoke erythema nodosum, and it is probable that it merely acts as a provocative agent in a predisposed individual.

CONCLUSIONS

In this group of 55 cases, there is a high incidence of children with a positive tuberculin test compared to the low incidence of children with a positive tuberculin test in the average population. While in many of these cases there is no conclusive proof that the erythema nodosum was of tuberculous origin, one must conclude that erythema nodosum occurs very commonly in association with tuberculosis and at various stages of the disease, or with an extension of the disease.

If Wallgren's [2] hypothesis is correct, that erythema nodosum occurs at the height of tuberculin sensitivity, it is not surprising that in 80% of the tuberculous erythema nodosum cases the patients had positive tuberculin test on admission to hospital. But some of these children, at the time of admission, had x-ray evidence of pulmonary or mediastinal disease, a few even with some calcification. Therefore, one must conclude that they had not just converted to a positive tuberculin reaction with

the appearance of this erythema nodosum. It is likely that erythema nodosum is the external sign of a change in tuberculin sensitivity, whether it is due to tuberculin conversion, or to an extension of the tuberculous process or to a depression of sensitivity during an infection, as one knows can occur in measles.

It is also evident from this series of cases and from the other series reported from this continent that erythema nodosum occurs almost as frequently with other diseases as with tuberculosis. Erythema nodosum does not develop in all cases of tuberculosis, hemolytic Streptococcus infections, coccidioidomycosis, and others; therefore, it is necessary to postulate that there must be a hereditary predisposition of certain individuals to respond to various infections in this manner. This individual response may become clear with further study and understanding of changes in the connective tissue system in various diseases.

HEMOLYTIC DISEASE OF THE NEWBORN DUE TO ABO INCOMPATIBILITY

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IT IS GENERALLY agreed that hemolytic disease of the newborn is usually caused by antibodies formed in Rhesus-negative mothers against the Rh factor D (Rh_0) of Rhesus-positive children. According to Wallerstein [1] this mechanism accounts for 92%, according to Mollison [2] for some 95%, of all cases of the disease. Of the remaining instances, a few are due to sensitization of the mother against one of the other Rh antigens or against an antigen belonging to a different blood group system such as Kell. This still leaves a residue of unexplained cases, and in many of these incompatibility of the major ABO blood groups has been held responsible.

By now a considerable number of instances of the disease attributed to maternal anti-A or anti-B antibodies has been recorded all over the world. In 1948, Grumbach and Gasser [3] fully reviewed the literature of the subject and added nine cases of their own. By the beginning of 1950, Jouvenceaux [4] was able to analyze some 30 observations and found that the condition was clinically and pathologically similar to that caused by Rh immunization. In the same year a large group of cases was published in Holland,[5] and by now over 100 examples of the condition have been recorded. In most of these cases, the mother belonged to group O and the infant to group A or, less commonly, to group B; the child's disease was thus considered to have been caused by maternal anti-A antibodies (or α) and anti-B antibodies (or β), respectively. The fact that anti-A was incriminated more often than anti-B is readily understood if one considers that group A occurs much more commonly than group B among the general population; in Britain their respective frequencies are about 41.7% and 8.6%.[6] In addition to the O-A or O-B relationship between

From the Children's Department, The London Hospital, London, England.

1. Wallerstein, H.: Blood, Spec. Issue No. 2, 1948, p. 170.

2. Mollison, P. L.; Mourant, A. E., and Race, R. R.: The Rh Blood Groups and Their Clinical Effects, Medical Research Council Memorandum No. 19, London, His Majesty's Stationery Office, 1948, p. 49.

3. Grumbach, A., and Gasser, C.: Helvet. paediat. acta **3**:447, 1948.

4. Jouvenceaux, A.: L'iso-immunisation maternelle aux agglutinogènes A et B et ses rapports avec la maladie hémolytique du nouveau-né, Thesis, Lyon, France, 1950.

5. Van Loghem, J. J., Jr.; van der Hart, M., and Paulussen, A. M. H.: Rev. hémat. **5**:371, 1950.

6. Dobson, A. M., and Ikin, E W: J Path & Bact **58**:221, 1946.

mother and child, it is also possible for the disease to occur when a group A mother has a B or AB child and when a B mother has an A or AB child, though such cases appear to be rare. The term "heterospecific pregnancy" is used nowadays for all these blood-group relationships where the infant has an A or B agglutinogen which the mother does not possess and against which she may have antibodies; about one pregnancy in every five is "heterospecific" according to this definition. It may be noted that the term was originally employed by Hirszfeld and Zborowski [7] in a wider sense to denote any pregnancy in which mother and child belonged to different ABO groups.

It has been pointed out repeatedly [8] that erythroblastosis due to ABO isoimmunization frequently affects first-born children, and in this respect it differs from that due to Rh incompatibility. It may be pertinent to remember that α and β agglutinins are ordinarily present in persons whose blood does not contain the corresponding agglutinogen and are thus already found in the mother at the beginning of her first pregnancy, while anti-Rh agglutinins are not normally encountered at that time, unless Rh-positive blood has been transfused previously.

Most cases of hemolytic disease due to anti-A and anti-B antibodies are said to be mild. However, instances have been reported in which even hydrops fetalis was considered to have been caused in this manner,[9] and kernicterus has been described repeatedly, though not always verified by autopsy.[10]

Estimates of the incidence of the condition vary widely. Allott and Holman [11] stated that isoimmunization to A or B blood group antigens occurred so rarely in cases of hemolytic disease as to be a curiosity. However, Polayes [9a] encountered it in 9 out of a personal series of 150 cases, i. e., in 6%, and others [12] found an even higher proportion. Wiener and colleagues [8b] considered ABO incompatibility to be the commonest cause of erythroblastosis in infants with Rh-positive mothers.

There are two main difficulties in estimating the true incidence of hemolytic disease caused by ABO antibodies. The first is that of definition, for the condition shades off into early "physiological" jaundice; the second is that of serological diagnosis, for this may be suggestive but is rarely conclusive.

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7. Hirszfeld, L., and Zborowski, H.: Klin. Wchnschr. **4**:1152, 1925.

8. (*a*) Boorman, K. E.; Dodd, B. E., and Mollison, P. L.: J. Obst. & Gynaec. Brit. Emp. **51**:1, 1944. (*b*) Wiener, A. S.; Sonn, E. B., and Hurst, J. G.: Wiener Laboratories Paper No. 1, July, 1946. (*c*) Van Loghem, Hart, and Paulussen.[5] (*d*) Roget, J., and Cau, G.: Pédiatrie **40**:709, 1951.

9. (*a*) Polayes, S. H., and Ohlbaum, C.: Am. J. Clin. Path. **15**:467, 1945. (*b*) Aubert, E. F.; Cochrane, J. B., and Ellis, M. E.: Brit. M. J. **2**:648, 1945. (*c*) Grumbach and Gasser.[3] (*d*) Franklin, R. T. D.; Newstead, P.; Pashley, M., and Roy, R. B.: Brit. M. J. **2**:680, 1950.

10. (*a*) Polayes, S. H.: Am. J. Dis. Child. **69**:99, 1945. (*b*) Grumbach and Gasser.[3] (*c*) Boorman, K. E.; Dodd, B. E., and Trinick, R. H.: Lancet **1**:1088, 1949. (*d*) Mitchell, N.; Moss, A. H.; Redner, B.; Levy, H., and Greenblatt, I. J.: Pediatrics **3**:813, 1949. (*e*) Ziegler, E.: Ann. pædiat. **172**:226, 1949. (*f*) Schwarz, J., and Speiser, P.: Wien. klin. Wchnschr. **62**: 63, 1950. (*g*) Jervis, G. A.: Am. J. Dis. Child. **79**:495, 1950. (*h*) Diamond, L. K.; Allen, F. H., and Thomas, W. O., Jr.: New England J. Med. **244**:39, 1951. (*i*) Halbrecht, I.: J. Pediat. **39**:185, 1951.

11. Allott, E. N., and Holman, C. A.: Lancet **1**:209, 1949.

12. Van Loghem, Hart, and Paulussen.[5] Roget and Cau.[8d]

ICTERUS PRAECOX

In 1944, Halbrecht [13] reported 60 instances of benign neonatal jaundice commencing within 24 hours of birth and unaccompanied by any blood change apart from occasional mild anemia. He called this condition "icterus neonatorum precox" and made the interesting observation that in 57 of the 60 cases, i. e., in 95%, the pregnancy was heterospecific as regards the ABO group and the child's red cells were agglutinated by the mother's serum. Among 160 control cases of ordinary "physiological" jaundice only 48, i. e., 30%, had a similar blood-group incompatibility, and among 2,000 neonates without any jaundice only 530, i. e., 26.5%, showed it. Halbrecht therefore concluded that early benign jaundice might be due to the passage of α and β agglutinins from the maternal circulation into the fetus. His findings were supported by Wiener and his colleagues [14] who investigated neonatal jaundice and anemia in infants with Rh-positive mothers. Again, Boorman and colleagues [15] found ABO incompatibility in 11 out of 18 infants in whom jaundice became apparent by the second day.

Recently Halbrecht [101] estimated the incidence of icterus praecox as 1 per 25 heterospecific pregnancies, which is proportionately similar to that of erythroblastosis fetalis in Rh incompatibility. He also described a family in which icterus praecox in the third child was followed by kernicterus in the fourth, attributed to maternal anti-A antibodies. He concludes that icterus praecox is only a mild form of hemolytic disease of the newborn. It would follow from this that the incidence of the disease due to ABO incompatibility is as high as that of the usually more severe form due to Rh antibodies. It is, however, a question of definition whether icterus praecox should be included in "hemolytic disease" as ordinarily understood.

SEROLOGICAL DIAGNOSIS

The evidence that hemolytic disease was indeed caused by anti-A or anti-B antibodies has often been very inadequate in the recorded cases. Not infrequently it was merely shown that the ABO groups of mother and infant were such as to allow of isoimmunization while the major Rh antigen was identical. Gradually it became apparent that incompatibility of the other Rh factors and of the remaining blood groups must also be excluded, and it became customary to adduce the evidence of a high or rising titer of anti-A or anti-B in the mother during pregnancy or in the puerperium. Further, a number of methods have been devised to demonstrate maternal immune antibodies, which differ from the ordinary α and β agglutinins. Another logical step was to try and trace the incompatible maternal antibodies in the infant's serum. Finally, attempts have been made to provide the strongest possible evidence, namely to demonstrate these antibodies acting on the baby's blood and tissues.

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13. Halbrecht, I.: Am. J. Dis. Child. **68**:248, 1944.

14. (*a*) Wiener, Sonn, and Hurst.[8b] (*b*) Wiener, A. S.; Wexler, I. B., and Hurst, J. G.: Blood **4**:1014, 1949.

15. Boorman, K. E.; Daley, D., and Dodd, B. E.: J. Obst. & Gynaec. Brit. Emp. **54**:281, 1947.

Serological methods of diagnosis in hemolytic disease of the newborn due to ABO incompatibility.

1. Demonstration of ABO incompatibility between mother and child with exclusion of any other maternal immunization
2. Demonstration of α or β isoagglutinin in high titer in the maternal serum
3. Demonstration of immune ABO antibodies in the maternal serum
   - I. Immune agglutinins, as shown by
     - (*i*) agglutination at higher titer in colloid media, or positive indirect Coombs test at higher titer, than agglutination in saline
     - (*ii*) persistence of agglutination in colloid media, or of positive indirect Coombs test, after inactivation of saline agglutinins by
       - (a) heating
       - (b) neutralization with A or B substance
     - (*iii*) shift in thermal optimum of agglutination to 37 C.
     - ? (*iv*) blocking test
   - II. Hemolysins, active at 37 C., and complement-fixing antibodies against A or B antigen
4. Demonstration of incompatible ABO antibodies in the infant
   - I. Presence of incompatible antibodies in the serum (and in the tissues after death)
   - II. Action of such antibodies on the infant's red cells as shown by
     - (*i*) positive direct Coombs test
     - (*ii*) different time of survival of red cells belonging to different groups

These steps must be discussed in some detail:

1. *Demonstration of ABO incompatibility between mother and child with exclusion of any other maternal immunization.*—Nowadays this requires a full investigation of the mother's and infant's blood groups. It must be demonstrated that the child's blood has A or B agglutinogen not possessed by the mother and that the maternal serum does not contain any atypical antibody as tested against a panel of group O cells representing all the Rh as well as MNS, P, Kell, Lutheran, Lewis, Kidd, and Duffy antigens. The antibody tests must be performed in saline and albumin media and are usefully supplemented by the indirect antihuman globulin technique.[16]

Special mention may be made of the useful evidence in this respect which may be supplied by binovular twins. Suppose the affected infant has a healthy twin whose blood groups are identical except for ABO. If then the maternal ABO group is incompatible with that of the affected twin but not with that of the unaffected one, this would obviously suggest that ABO antibodies caused the disease.

2. *Demonstration of α or β agglutinins in high titer in the maternal serum.*—It is well known that normal persons have anti-A or anti-B agglutinins in their serum if the corresponding agglutinogens are not present in their red cells (Landsteiner's Law). The titer of these normal isoagglutinins given by different investigators varies according to their techniques; thus Schwarz and Speiser [10f] state that it averages 40 and Wiener and Moloney [17] found that it exceeds 60 in only 5% of normal persons, while Mollison and Young [18] placed the average at 64 to 128. It was first shown by Dienst [19] that the titer of these antibodies may rise in a pregnant woman if the infant possesses the corresponding agglutinogen.

16. Coombs, R. R. A.; Mourant, A. E., and Race, R. R.: Lancet **2**:15, 1945.
17. Wiener, A. S., and Moloney, W. C.: Am. J. Clin. Path. **13**:74, 1943.
18. Mollison, P. L., and Young, I. M.: Lancet **2**:635, 1941.
19. Dienst, A.: Zentralbl. Gynäk. **29**:353, 1905.

There is disagreement in the literature concerning the proportion of women whose agglutinin titer will rise in heterospecific pregnancy. However, most recent authors consider such a rise as common. Smith [20] found a rise in 40 out of 46 heterospecific pregnancies, compared to only 1 out of 154 homospecific ones. He also made the important observation that only those infants immunized their mothers who "secreted" A or B blood group substance in their tissue fluids; such secretion is known to occur in about 80% of Europeans. The maximum maternal agglutinin titers reached were 12,800 for anti-A and 8,000 for anti-B, yet there was no evidence of any harmful effect upon the child. Boorman, Dodd, and Mollison [21] detected a rise in the relevant maternal isoagglutinin titer in 36 out of 44 cases of heterospecific pregnancy; the titers increased from 4 to over 64 times. Most of the increase occurred after delivery, and peak titers were usually reached between the 10th and 20th days of the puerperium. Some of the maximum titers exceeded 256,000. Polayes and McNally [22] also showed that pregnancy caused a rise in isohemagglutinin titers, particularly in heterospecific cases, but their highest figures were only 20,000 in two cases. Schwarz and Speiser [10f] found in 300 postpartum patients that the average titer of α and β was more than double the normal value, while the maximum was 1024 by their technique; higher values (up to 128,000) were found in 10 cases in which the infant appeared to suffer from hemolytic disease.

It can be seen from all this that a rise in maternal isohemagglutinin titer per se represents poor evidence for a diagnosis of hemolytic disease of the newborn due to ABO antibodies, for such a rise may occur normally in heterospecific pregnancy. One can merely state that a rise of titer to high figures is more likely to be associated with hemolytic disease in the infant than a normal level. Yet a low or normal maternal agglutinin titer does not disprove the diagnosis, as the antibody may be qualitatively abnormal or the child's defenses inadequate. Several authors have actually reported cases of erythroblastosis fetalis due to ABO antibodies in which the mother's titers were within normal limits. Others have found very high figures. Aubert and colleagues [9b] encountered an infant with gross hydrops fetalis attributed to anti-A, whose mother had agglutinins against standard A_1 cells to the extraordinary level of 1:16,000,000, and in Weisl's [23] case of neonatal anemia the mother's anti-A titer even reached 82,000,000. Such figures are impressive, but it should be mentioned that Wiener and colleagues [14b] doubt the accuracy of very high values and consider them due to faulty technique, especially "carrying over" in making dilutions. They argue that such high titers would necessitate the presence of an impossibly large amount of serum globulin in the form of antibody.

3. *Demonstration of maternal immune ABO antibodies.*—In heterospecific pregnancy and after incompatible blood transfusion immune ABO antibodies are liable to be formed which differ from ordinary isoagglutinins. Such immune antibodies may be broadly divided into immune agglutinins and hemolysins.

I. *Immune agglutinins.*—These are somewhat analogous to the incomplete agglutinins in Rh incompatibility. In the latter condition it is well known that such antibodies (which Wiener calls univalent) can be most easily demonstrated either by their action in blocking ordinary agglutination in saline or by their property of

20. Smith, G. H.: J. Path. & Bact. **57**:113, 1945.
21. Boorman, K. E.; Dodd, B. E., and Mollison, P. L.: J. Path. & Bact. **57**:157, 1945.
22. Polayes, S. H., and McNally, J., Jr.: Am. J. Clin. Path. **18**:375, 1948.
23. Weisl, B. A. G.: Am. J. Obst. & Gynec. **56**:1000, 1948.

agglutinating the corresponding red cells only in albumin or similar media which probably take part in the reaction. In ABO incompatibility the presence of natural isoagglutinins makes it difficult to demonstrate immune agglutinins unless, first, the latter are active to a higher titer, or, second, isoagglutinins can somehow be inactivated. A third, more indirect, procedure is to demonstrate a shift in the thermal optimum for agglutination from the normal (4 to 10 C.) to 37 C. Fourth, the blocking test has sometimes been used to demonstrate immune anti-A or anti-B agglutinins.

(*i*) Anti-A or anti-B agglutinins reaching their highest titers in colloid media have often been encountered. Boorman, Dodd, and Morgan [24] first demonstrated the presence of immune ABO hemagglutinins in heterospecific pregnancy and after incompatible transfusion by the fact that the addition of human serum enhanced agglutination. Serum appears to be a better activating agent for immune ABO agglutinins than albumin or plasma-albumin mixture. Wiener and colleagues [14b] obtained the highest titers by using a suspending solution containing acacia. Gelatin and polyvinylpyrrolidone have also been found effective as activators,[25] but may give nonspecific reactions at high titer.[26]

Many authors have endeavored to prove the diagnosis of erythroblastosis fetalis due to ABO incompatibility by showing that the maternal agglutinin titer in serum (or similar medium) exceeded the titer in saline, or, to express it in Wiener's terminology, that the titer of conglutination was higher than that of agglutination. Wiener,[8b] Gruber,[27] and Grove-Rasmussen [28] and their respective colleagues were some of the first to use this test in their cases. Again, as with the ordinary isoagglutinins, some very high titers have been reported, for instance in Grumbach and Gasser's [8] second and sixth cases and in Ziegler's [10e] patient.

Another way of demonstrating immune antibody at a titer higher than that of ordinary isoagglutinins is by the use of the antiglobulin technique (indirect Coombs test), and this method may deserve further study, though Wiener and colleagues [14b] did not find it satisfactory in ABO cases.

Yet another test may be considered to represent the converse of the enhancement of titration by colloid media. Gurevitch and colleagues [29] found that physiological ABO antibodies gave no difference in titration when tested with washed and unwashed red cells, whereas immune antibodies showed distinctly higher titers when titrated with unwashed than with washed red cells. The authors suggested that washing probably freed the red cells from some of the serum proteins present in the suspension and that these proteins tended to raise the titer of reaction with immune antibodies.

(*ii*) To neutralize or eliminate the ordinary isoagglutinins and thus to allow the demonstration of immune antibodies at a low titer various methods have been devised. Boorman and Dodd [30] heated two immune anti-A sera for 20 minutes at approximately 75 C. and found that thereafter agglutination of A_1 cells at room

24. Boorman, K. E.; Dodd, B. E., and Morgan, W. T. J.: Nature, London **156**:663, 1945.
25. Spielmann, W.: Klin. Wchnschr. **29**:13, 1951.
26. Mourant, A. E.: Personal communication to the author.
27. Gruber, S.; Litvak, A., and Jacobi, M.: J. Pediat. **29**:518, 1946.
28. Grove-Rasmussen, M.; Tudvad, F., and Jørgensen, G.: Nord. med. **38**:1259, 1948.
29. Gurevitch, J.; Polishuk, Z., and Hermioni, D.: Am. J. Clin. Path. **19**:265, 1949.
30. Boorman, K. E., and Dodd, B. E.: Nature, London **158**:589, 1946.

temperature no longer occurred, while the blocking and indirect Coombs tests were still positive. It has also been shown that after similar heating the presence of immune agglutinins can be demonstrated by persistent agglutination in a serum, though not in a saline, medium.[12] Further, the use of dialysis has been suggested to separate ordinary from immune agglutinins [31] but has not apparently been successful as yet. Perhaps the most ingenious method is that of Witebsky [32] who found that isoagglutinins could be neutralized by A or B substance, respectively, and that immune agglutinins could then still be demonstrated if serum was used as a diluent. The presence of immune agglutinins as shown by this test appeared to provide evidence of isoimmunization, and Witebsky considered that a very high titer of ordinary isoantibodies was neither essential nor necessarily indicative of immunization against the A or B factors. Mitchell and colleagues [10d] used Witebsky's method to demonstrate immune anti-A agglutinins in their third case of hemolytic disease resulting from anti-A isoimmunization, and Witebsky [33] himself demonstrated potent immune anti-A in a fatal case in this manner.

Ervin, Christian and Young [34] extended Witebsky's technique by showing that immune anti-A serum after partial neutralization with A substance would still give a positive indirect Coombs test, i. e., would sensitize A_1 cells to antihuman-globulin serum, even though it would no longer agglutinate them suspended in saline. Mollison [35] finds this method a more convenient way of demonstrating immune agglutinins than the titration of neutralized serum against cells suspended in serum.

Another possible modification of Witebsky's method may be the demonstration that an immune serum continues to agglutinate red cells treated with trypsin,[36] after ordinary isoagglutinins have been neutralized; but this technique requires further study.

(*iii*) Natural α and β agglutinins usually attain distinctly higher titers at refrigerator than at incubator temperature. In 1941 Wiener [37] noted that the thermal optimum of anti-A agglutinins was raised in an individual who had had an incompatible transfusion. The upward shift in the thermal optimum to 37 C. as a feature of the immune response to A or B antigen has since been emphasized by Hubinont.[38] It has been confirmed in cases of hemolytic disease reported by others.[39]

(*iv*) The blocking test appears to have been performed by few authors, and Wiener and his colleagues [14b] considered that it could not be used in ABO isoimmunization. However, "zoning" has been observed [30] in agglutination by immune anti-A sera, and Van Loghem and colleagues [5] demonstrated the presence of blocking antibodies in the majority of eight absorbed immune sera.

31. Wiener, Wexler, and Hurst.[14b] Spielmann.[28]

32. Witesbsky, E.: Blood, Spec. Issue No. 2, p. 66, 1948.

33. Witebsky, E.: Federation Proc. **8**:414, 1949.

34. Ervin, D. M.; Christian, R. M., and Young, L. E.: Blood **5**:553, 1950.

35. Mollison, P. L.: Blood Transfusion in Clinical Medicine, Oxford, England, Basil Blackwell & Mott, Ltd., 1951, pp. 150-179, and 388-393.

36. Morton, J. A., and Pickles, M. M.: Nature, London **159**:779, 1947.

37. Wiener, A. S.: J. Immunol. **41**:181, 1941.

38. Hubinont, P. O., and Millet, M.: Gynéc. et obst. **45**:718, 1946. Hubinont, P. O.: Brit. M. J. **2**:574, 1949.

39. (*a*) Heffinck, R.: Presse méd. **55**:823, 1947. (*b*) Seigneurin, R.; Roget, J.; Groulade, J., and Viallat, F.: Presse méd. **58**:939, 1950. (*c*) Seigneurin, R., and Groulade, J.: Sang **22**:223, 1951.

II. *Hemolysins.*—Jonsson [40] first showed on a large scale that hemolysins ("isolysins") against A or B cells tended to appear in maternal sera as a result of heterospecific pregnancy. These lysins are also encountered after incompatible transfusions. A number of authors have demonstrated such hemolysins in the maternal sera in cases of hemolytic disease of the newborn,[41] and Mollison [35] considers their presence a characteristic feature resulting from isoimmunization.

Witebsky [32] showed that the sera of immunized patients may fix complement when mixed with material containing water-soluble A or B substance. Similarly, Ervin and Young [42] found that immune anti-A serum fixed complement when added to A cells. The fixation of complement may well be connected, or even identical, with hemolysis.[35]

The appearance of immune antibodies in the mother during pregnancy may be accepted as evidence of immunization by the fetus. However, such antibodies probably arise normally in a proportion of heterospecific pregnancies without necessarily causing any harm to the infant. Witebsky [33] investigated 50 such pregnancies for maternal immune agglutinins by his neutralization technique. Varying degrees of immune antibody formation were demonstrated in a minority of the mothers. However, even in the few instances in which a potent antibody of this kind was found the baby proved normal on delivery. He concluded that the presence of immune antibodies in the mother's serum was insufficient evidence to predict the occurrence of erythroblastosis in the newborn.

In confirmation of these findings I may quote the case of a patient encountered recently. This was an Rh-positive woman, aged 44 years, who was pregnant for the 11th time. She belonged to group O and her Rh-negative infant to group A. Fourteen days after delivery the mother's serum was tested by Dr. Dorothy M. Parkin and found to agglutinate A cells to a titer of 512 at room temperature and 1000 at 37 C. in a serum-albumin mixture, after all anti-A as titrated in saline had been neutralized by absorption with A substance. The corresponding titers against B cells were only 0 and 2, respectively. The indirect Coombs test after absorption was positive with A_1 cells and negative with B cells. The infant became only mildly jaundiced three days after birth and remained perfectly well.

Again, immune anti-A agglutinins have occasionally been demonstrated in the sera of pregnant women, although the child was eventually found to belong to group O and to be unaffected by hemolytic disease. In some such cases the immune antibodies may be residual from previous pregnancies ending in the birth of group A children.[43] However, immune antibodies have even been found in a small proportion of random sera from the general population. One group of investigators [34] demonstrated small amounts of immune anti-A agglutinins in 12 out of 100 group O sera; in another series [44] it was shown that 18% of a sample of 125 group O sera contained appreciable amounts of α hemolysin and that α and β hemolysins were usually accompanied by incomplete agglutinins.

40. Jonsson, B.: Acta path. et microbiol. scandinav. **13**:424, 1936.

41. Tortora, M.: Arch. ostet. e ginec. **53**:436, 1948. Boorman, Dodd, and Trinick.[10e] Schwarz and Speiser.[10f]

42. Ervin, D. M., and Young, L. E.: Blood **5**:61, 1950.

43. Witebsky.[32] Jouvenceaux.[4]

44. Crawford, H.; Cutbush, M.; Falconer, H., and Mollison, P. L.: Lancet **2**:219, 1952.

It may be true that hemolytic disease of the newborn due to ABO incompatibility never occurs in the absence of maternal immune anti-A or anti-B antibodies. But the converse does not hold, and maternal immune antibodies do not necessarily cause erythroblastosis fetalis in the child. Thus, when there is evidence of hemolytic disease of the newborn and the only demonstrable incompatibility between the blood of mother and child is in the ABO group, then the presence of immune antibodies in the mother will suggest that they are to be blamed for the child's disease, but this suspicion does not amount to positive proof.

4. *Demonstration of incompatible antibodies in the infant.*—If a maternal antibody liable to damage the infant's red cells can actually be demonstrated in the child's blood after birth, then the case for hemolytic disease being caused by this antibody is considerably strengthened. In erythroblastosis due to ABO incompatibility such agglutinins were first found in the cord blood by Aubert and colleagues.[9b] In later cases, when incompatible antibodies were thus encountered they were usually of the immune type and could not be demonstrated in saline at all or only at a lower titer.[45] Incompatible immune anti-A agglutinins, which may admittedly have been reinforced by transfusions of group O blood, were still present in one affected infant 80 days after birth [46]; in another child, who had only received group A blood, they were still demonstrable at 60 days.[28] The presence of antibodies may also be revealed by the fact that the infant's serum gives a positive indirect Coombs test against cells of his own group.

Again one wonders how often such incompatible agglutinins may penetrate into the infant's circulation in heterospecific pregnancy without doing any harm. Unfortunately most of the investigations on this point have only been concerned with ordinary agglutinins in saline. With regard to these most authors agree that incompatible antibodies can only rarely be demonstrated in the infant's blood. Hirszfeld and Zborowski [7] first pointed this out; for instance, in the O-A relationship between mother and child they only found significant amounts of anti-A in the cord blood in 1 out of 26 cases, and in the O-B relationship significant anti-B in the cord blood in none of 11. More recently Jakobowicz and Bryce [47] investigated 355 samples of cord blood and the corresponding maternal blood. Among these 355 there were 79 derived from heterospecific pregnancies, in which the infant possessed A or B agglutinogens absent from the mother. In only 4 of these 79 did the authors find agglutinins in the cord blood which were antagonistic to the child's red cells. One of the four infants in question was two months premature and died within 24 hours; the other three developed quite normally, only one showing "physiological" jaundice.

Thus we see that incompatible ordinary ABO isoagglutinins may be present in the newborn infant's serum in low titer without causing any damage, but their presence is uncommon. It may well be shown that immune agglutinins penetrate more readily than simple agglutinins into the child's circulation in heterospecific pregnancy, as has been found in compatible pregnancies and in Rh incompatibility,[48]

45. (*a*) Footnotes 28, 10 *d*, 14 *b*, and 33. (*b*) Robinson, G. C.; Phillips, R. M., and Prystowsky, M.: Pediatrics **7**:164, 1951.

46. Provenzano, R. W.: Connecticut M. J. **15**:476, 1951.

47. Jakobowicz, R., and Bryce, L. M.: M. J. Australia **1**:669, 1948.

48. Wiener, Wexler, and Hurst.[14b] Loghem, Hart, and Paulussen.[5]

but this remains a matter for investigation. Meanwhile the presence of incompatible anti-A or anti-B in the infant's serum must be considered as unusual and as a potential cause of neonatal hemolytic disease.

The best serological evidence for hemolytic disease of the newborn is to demonstrate not only the presence but the action of incompatible antibodies in the infant. This can be done most simply by using the antiglobulin technique and thus showing that the child's red cells are coated by antibody. In cases of the disease attributed to ABO incompatibility, a positive direct Coombs test in the affected child has been recorded occasionally.[49] Also, among 209 Rh-compatible pregnancies with ABO incompatibility, Jakobowicz and colleagues [50] obtained three instances of a positive Coombs test on the cord blood, and two of the three infants concerned also had jaundice or anemia or both, while in all three cases there was a marked rise of maternal isoagglutinin titer. On the other hand, these authors encountered 10 infants who showed similar clinical findings with the same blood group relationship and yet had negative Coombs tests. If positive, the test is certainly valuable evidence of hemolytic disease. It has, however, the following two imperfections: First, it does not indicate the specific nature of the offending antibody; second, it is not so sensitive for anti-A and anti-B as for anti-Rh antibodies and may be negative if the cells are only weakly sensitized by α or β agglutinin. The latter fact was noted by Coombs, Mourant, and Race in their original communication on the direct antiglobulin test in 1946.[51] It has encouraged authors to attribute cases of hemolytic disease to ABO incompatibility even when the direct Coombs test on the infant's blood was negative.[52] While a negative test does not exclude the disease, the supporting evidence will then have to be particularly good for the diagnosis to be accepted.[53] A positive test strongly supports the diagnosis but requires complementary proof to show that the coating antibody is an ABO agglutinin. It is possible to elute the antibody from sensitized cells by heating at 56 C. as has been done for Rh antibodies [53a]; the specific nature of the agglutinins may then be ascertained.

In isolated instances research workers have brought forward even better evidence for the damaging action of ABO antibodies in hemolytic disease. Thus Boorman and colleagues [10c] recovered anti-A from the tissue cells of a group A infant who had died with kernicterus on the fourth day of life. The authors cautiously point

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49. (*a*) Boorman, Dodd, and Trinick.[10c] (*b*) Mollison, P. L., and Cutbush, M.: Lancet **2**:173, 1949. (*c*) Berndt, H., and Feldmann, F.: Klin. Wchnschr. **29**:209, 1951. (*d*) Zoutendyk, A., and Broido, A.: Brit. M. J. **1**:1357, 1951. (*e*) Provenzano.[46]

50. Jakobowicz, R.; Krieger, V. I., and Simmons, R. T.: M. J. Australia **2**:143, 1948.

51. Coombs, R. R. A.; Mourant, A. E., and Race, R. R.: Lancet **1**:264, 1946.

52. (*a*) Christiaens, L., and Goudemand, M.: Semaine hôp. Paris **26**:3336, 1950. (*b*) Spielmann.[28] (*c*) Robinson, Phillips, and Prystowsky.[45b] (*d*) Provenzano.[46]

53. Various modifications of the Coombs test are under trial in order to increase its specificity or the incidence of positive reactions. A notable method is the two-stage antiglobulin reaction recently devised by Dr. Alan Richardson Jones, of Boston. This is reported to be positive in the majority of infants with hemolytic disease due to ABO incompatibility, even when the direct Coombs test performed by the ordinary technique, is negative (personal communication to the author).

53a. Zuelzer, W.; Wheeler, W. E., and Leonard, M., in Discussion on Rh Factor: Practical Aspects, Pediatrics **1**:799, 1948.

out, however, that the finding of antibodies in tissue eluates still does not prove that they became attached to the cells during life or caused tissue damage. Perhaps the most convincing evidence of all was supplied in these authors' other case, in which the rapid destruction of group A red cells with normal survival of group O cells was demonstrated in the circulation of an anemic infant. Similar proof was recorded in isolated cases by Mollison and Cutbush [49b] and by Chaptal and colleagues.[54] While these procedures are the best diagnostic evidence they are unfortunately impracticable in ordinary hospital laboratories.

To summarize: The presence of a greatly raised maternal anti-A or anti-B agglutinin titer and/or the demonstration of immune ABO antibodies in the mother are suggestive of the diagnosis in the presence of a characteristic clinical and hematological picture in the child, when other incompatibilities have been excluded. Better evidence is supplied by showing that the incompatible antibodies are present in the infant, particularly if their action can be demonstrated, at least by a positive direct Coombs test.

The subject is summed up succinctly by Race and Sanger [55]:

> That a mother can be immunized to foetal A or B is undoubted; but whether the immune anti-A or anti-B ever causes haemolytic disease is still a matter of argument, though the opinion is growing amongst experts that, on rare occasions, it can . . . In order to make an impressive case for anti-A or anti-B it is necessary to exclude all the Rh antigens including C^w, and to exclude the Kell antigen. Moreover it is necessary to demonstrate in vivo sensitization of the red cells of the newborn baby by means of the direct antiglobulin test.

Few of the recorded cases fulfil these criteria.

CASE RECORD

It is now intended to record the occurrence of hemolytic disease, probably due to anti-B antibodies, in binovular twins. Their cases are of interest as an illustration of some of the diagnostic methods and also because the disease was of different severity in the two infants and led to kernicterus, verified at autopsy, in one of them, while the other made a full recovery.

The mother was a healthy primigravida aged 25 years. She was a twin herself and had twin cousins and twin uncles. She had had no notable diseases in the past and had never received any transfusions or injections of blood or serum. Her last menstrual period had occurred on Oct. 3, 1949. The pregnancy was normal apart from morning vomiting during the first three months, slight vaginal bleeding in the second and third months, and edema of the ankles in the eighth month. She attended an antepartum clinic and was found to be Rh positive; her blood Kahn test proved negative.

She was admitted to hospital on June 5, 1950, as her membranes had ruptured spontaneously during the preceding night. A twin breech presentation was diagnosed. As she did not have any pains, labor was induced medically three days later; it lasted five hours and terminated in delivery under trichloroethylene and oxygen anesthesia in the afternoon (June 8th). Forceps were used on the aftercoming heads, and two small female infants were extracted who differed in appearance and had separate placentae with double layers of membranes.

Twin 1 was cyanosed at birth and did not breathe well for about three minutes while mucus and amniotic fluid were sucked from the throat and oxygen therapy was given. Thereafter she cried vigorously and gained a normal color. Her weight was 4 lb. 15 oz. (2,240 gm.). About

54. Chaptal, J.; Cazal, P.; Brunel, D.; Graafland, and Salvaing, J.: Arch. franç. pédiat. 8:43, 1951.

55. Race, R. R., and Sanger, R.: Blood Groups in Man, with Foreword by R. A. Fisher, Oxford, England, Basil Blackwell & Mott, Ltd., 1950, p. 232.

one hour after birth she was noticed to be slightly icteric. The jaundice increased progressively during the following days, and she appeared a little drowsy but took feeds and sucked at the breast. On the day after birth her skin-prick hemoglobin concentration [56] was 99%. The spleen did not become palpable and the liver was not abnormally large.

Five days after birth (on June 13th) she became more drowsy and had to be fed by tube. Her cry became highpitched, and there was slight head retraction. The presence of kernicterus was suspected. A number of investigations were undertaken (see Tables), and the infant's direct Coombs test was found to be positive, but no treatment appeared indicated at this stage apart from sedation with chloral hydrate.

The signs of cerebral irritation continued for three days. Seven days after birth (on June 15th) the child appeared limp and very ill and tended to vomit after tube feeds. The respirations were shallow and irregular, and oxygen had to be administered. The urine contained bile pigments. On the following day her condition began to improve, and by June 17th she had regained her ability to suck and cried normally. Her weight had fallen to 4 lb. 6½ oz. (2,000 gm.), but rose again from that day. On June 19th she was put back on the breast for the first time; she sucked quite well but tended to cry during feeds. By June 22d, her jaundice had begun to fade, and she appeared quite alert, though tending to hold her head back. Her serum bilirubin on that day was estimated at 19.9 mg. per 100 cc.

TABLE 1.—*Blood Groups* *

Father.....	B †	Rh positive; c, D, E, and e present, C absent, therefore probable genotype R₂r (cDE/cde)
Mother.....	O	Rh positive; C, c, D, E, and e all present therefore probable genotype R₁R₂ (CDe/cDE)
Both twins.....	B	Rh positive; c, D, E, and e present, C absent, therefore probable genotype R₂r (cDE/cde)

* The Rh genotyping was performed by Dr. I. A. B. Cathie and his staff at the Hospital for Sick Children, Great Ormond Street, London.

† Testing with anti-O serum suggests genotype BO; parents dead.

Twenty-six days after birth, on July 4th, she was discharged home with her mother and twin sister. At that time she weighed 4 lb. 13 oz. (2,185 gm.), and thus had not yet regained her birth weight. She was still faintly jaundiced and tended to cry with apparent colicky pain during and after feeds.

She was subsequently observed as an outpatient. Her weight gain was slow compared to that of her twin, and she continued to have frequent "colics," in which she cried vehemently and arched her back. Sometimes she screamed continuously for several hours. She appeared to take no notice of her surroundings, and though she moved her eyes she did not respond to light or noise. At the age of 2½ months the limbs were first found to be hypertonic and the cry to be whining.

When aged 4½ months she was readmitted to hospital for 11 days. She had not yet begun to smile and now weighed 10 lb. 3 oz. (4,620 gm.). She tended to keep her head retracted and turned to the right and was unable to hold it up. There was also some lid retraction, especially on change of posture. At times she protruded her tongue repeatedly for several minutes. Frequent rapid jerky choreiform movements of the head and limbs were now present, most marked in the right arm. There was generalized hypertonus, the tendon reflexes were brisk, and a crossed adductor response was observed in the right leg on eliciting the left knee jerk. When she cried there was increased head retraction and arching of the back with extension of the arms. Feeds were taken slowly, and the weight remained stationary while in the hospital.

When aged 8 months she weighed 12 lb. 3 oz. (5,530 gm.) and had begun to smile, but was still unable to hold up her head or to recognize objects or persons. Choreiform jerking of head and limbs and "tromboning" of the tongue were noted further.

56. This was estimated by the alkaline-hematin method with photoelectric colorimetry throughout; 100% signifies 14.8 gm. hemoglobin per 100 ml.

TABLE 2.—*Maternal Serum Antibodies*

Simple Agglutinins	No. of Days After Delivery	Anti-B Titer (in Saline at Room Temperature)	Anti-A Titer (in Saline at Room Temperature)
	5	4,096	...
	13	16,384	512
	22	32,000 *	...
	61	4,000	...
	109	128	64
	161	64	...

Immune Agglutinins †

1. Specimen taken 22 days after delivery (tested after eight months' deep freeze storage at —60 C. [—76 F.]).

(*i*) Titrations of serum against B cells at bench temperature before and after partial neutralization with equal parts of B secretor saliva.

Before Neutralization		After Neutralization		
Titer in Saline Against Cells Suspended in Saline	Titer in AB Serum Against Cells Suspended in 20% Bovine Albumin	Titer in Saline	Titer in Serum/Albumin	Indirect Coombs Test with B rr Cells
1,000	256	0	128	Positive

(*ii*) Titrations of serum against A cells at bench temperature before and after partial neutralization with equal parts of A secretor saliva.

Before Neutralization		After Neutralization		
Titer in Saline Against Cells Suspended in Saline	Titer in AB Serum Against Cells Suspended in 20% Bovine Albumin	Titer in Saline	Titer in Serum/Albumin	Indirect Coombs Test with A_1 Cells
64	32	0	0	Negative

2. Specimen taken 22 days after delivery. (Tested after 18 months' deep-freeze storage.)

Titration of serum against B cells at 37 C. and 20 C. before and after partial neutralization with B secretor saliva.

Before Neutralization				After Neutralization			
At 37 C.		At 20 C.		At 37 C.		At 20 C.	
Titer in Saline Against Cells in Saline	Titer in AB Serum Against Cells in AB Serum	Titer in Saline	Titer in Serum	Titer in Saline	Titer in Serum	Titer in Saline	Titer in Serum
512	8,000	256	256	0	2,000	0	256

3. Specimen taken 161 days after delivery (tested within two days).

Titration of serum against B cells at bench temperature before and after partial neutralization with B secretor saliva.

Before Neutralization		After Neutralization		
Titer in Saline Against Cells in Saline	Titer in AB Serum Against Cells in 20% Bovine Albumin	Titer in Saline	Titer in Serum/Albumin	Indirect Coombs Test with Brr Cells
64	32	0	8	Positive

Anti-B Hemolysin †

Specimen taken 22 days after delivery (tested after 18 months' deep freeze storage).

Serum titrated in saline; fresh human complement added.

Anti-B hemolysin demonstrated to a titer of 8 at 37 C.

Rh Agglutinins

No. Days	No Antibodies Against	Indirect Coombs Test Negative Against
5	O R_1R_2 cells or Orr cells in saline or albumin at 37 C.	Same cells
13	O R_1R_2 cells or Orr cells in saline or albumin at 37 C.	Same cells
22 †	Panel of O cells covering all Rh subdivisions in saline or albumin at 37, 20, 12, and 4 C.	Same panel of cells
61 ‡	O R_1R_2 cells or Orr cells in saline or albumin at 37 C.	O R_1R_2 cells
161 †	Panel of O cells covering all Rh subdivisions in saline or albumin at 37, 20, 12, and 4 C.	Same panel of cells

Other Antibodies

No. Days After Delivery	
22 †	No MNS, P, Lewis, Lutheran, Kell, Duffy, or Kidd antibodies in saline or albumin at 37, 20, 12, and 4 C.
61 ‡	No MN, P, Lewis, Lutheran, or Kell antibodies in saline or albumin at 37 or 20 C.
161 †	No MNS, P, Lewis, Lutheran, Kell, Duffy, or Kidd antibodies in saline or albumin at 37, 20, 12, or 4 C.

* Indirect Coombs test weakly positive beyond this dilution (at 1:64,000).

† These tests were performed by Dr. Dorothy M. Parkin at the Blood Group Reference Laboratory of

‡ This specimen was tested by Miss B. E. Dodd at the South London Blood Transfusion Centre (Director: Dr. R. A. Zeitlin).

At the age of nearly 9 months she had a series of generalized convulsions and died suddenly at home on March 7, 1951.

The autopsy was carried out by the coroner's pathologist (Dr. J. W. Lacey) on the following day. Externally, the infant's head was found to be slightly asymmetrical and the abdomen rather distended. On internal examination, the meninges were normal, and the brain was soft without any obvious macroscopic abnormality. A small amount of inhaled partly digested milk was present in the trachea and bronchi, and there was diffuse patchy peribronchial consolidation throughout both lower lobes of the lungs with intervening areas of partial collapse; the pleurae were normal. The liver was pale with early cloudy swelling. The spleen was normal in size but congested, with prominent Malpighian bodies. The remaining organs showed no abnormality. Bronchopneumonia was considered to be the immediate cause of death.

Further examination of several organs was carried out at the Bernhard Baron Institute of Pathology of The London Hospital by Dr. D. J. O'Brien. The brain weighed 1 lb. 9 oz. (0.78 kg.); there was no jaundice or other abnormality in coronal sections; the normal-sized third and lateral ventricles were lined by smooth ependyma. On microscopical examination, however,

TABLE 3.—*Hematological and Serological Investigations on the Twins*

	Age, Days	Twin 1	Twin 2
Hemoglobin concentration *	1	99%	....
	6	103%	80%
	7	103% †	88%
	9	96%	83%
	18	80%	76%
	25	67%	70%
	35	72%	67%
	61	85%	....
	77	92%	90%
Direct Coombs test	6	Positive	Positive
	14	Negative	....
Anti-A or anti-B agglutinin in serum	14	Absent	....
Secretion of B substance in saliva	140	Present β-agglutinin absorbed from grouping serum; titer reduced from 16 to 1	Present β-agglutinin absorbed from grouping serum; titer reduced from 64 to nil

* The alkaline hematin method of estimation with photoelectric colorimetry was used throughout; 100% signifies 14.8 gm. hemoglobin per 100 ml.

† No immature red cells were seen in the blood film on this day.

the globus pallidus and corpora Luysii were grossly abnormal; neurones were greatly diminished in number, only a very few mineral-encrusted cells remaining. In these areas there was advanced diffuse gliosis; this was particularly conspicuous in the globus pallidus. There was no abnormality in the putamen, caudate nucleus, internal capsule, thalamus, red nucleus, substantia nigra, lateral geniculate body, cornu ammonis, dentate nucleus, cerebellar cortex, or cerebral cortex.

Microscopy also showed slight fatty degeneration of the liver; endochondral ossification and hemopoiesis were normal in a rib; spleen, adrenal, and kidney were normal.

Twin 2 was only slightly cyanosed at birth and breathed as soon as the cord was cut. She was somewhat bigger than her sister and weighed 5 lb. 8 oz. (2,500 gm.). Apart from mild left-sided talipes calcaneovalgus she presented no abnormal signs. Slight jaundice was first noted on the second day, but the infant appeared healthy and sucked well at the breast. The jaundice gradually deepened and had become marked by the fourth day.

Five days after birth, when the first twin showed signs of cerebral irritation, the second appeared slightly lethargic and her spleen was just palpable. She was given alternate breast and bottle feeds, which were taken satisfactorily. Urinalysis revealed no abnormality. On the following day (June 14th) her direct Coombs test was found to be positive and her skin-prick hemoglobin concentration to be 80%, i. e., considerably lower than her sister's (Table 3). Her general condition was unchanged.

At the age of 7 days, when the first twin was very ill and required oxygen therapy, the second also had her worst day. She appeared more lethargic, and in the evening her cry sounded highpitched, and she had slight head retraction. However, she was still able to suck. The next day (June 16th) her condition was much improved and her jaundice began to diminish. From that day her weight, which had fallen to 4 lb. 15 oz. (2,240 gm.), commenced to rise, and her progress was satisfactory, though her hemoglobin concentration fell to 67% at the age of 5 weeks. She regained her birth weight after 20 days and took feeds well without crying. On discharge after 26 days she had lost all her jaundice and weighed 5 lb. 14 oz. (2,565 gm.); the spleen was no longer palpable.

She was then observed as an outpatient, together with the first twin. The difference in weight between them increased steadily. At the age of 2½ months the second twin weighed 10 lb. 9 oz. (4,790 gm.). She was now able to hold up her head and took notice of lights and noises. A few days later she began to smile.

At 4½ months, when the first twin was readmitted to hospital, the second had full ocular coordination and would turn her head towards a voice. At 8 months, she weighed 18 lb. 7 oz. (8,365 gm.) and was beginning to sit up. Her development was thus considered to be normal, as far as one can judge at this age.

The investigations have been listed in the tables. As regards the blood groups it will be seen that the only Rh antigens which the mother was not demonstrated to possess were C^w and d, and her serum contained no antibodies against these or any of the lesser blood groups. This leaves her anti-B as the only demonstrable antibody which could have played a part in the hemolytic disease of the infants. She had β-agglutinin in her serum in high titer, rising to a maximum of 32,000 twenty-two days after delivery. The further tests showed that an immune form of anti-B was also present, for

(*i*) The indirect Coombs test with B cells was positive at an even higher dilution than the maximum direct agglutination titer,

(*ii*) Residual agglutinins against B cells were demonstrated in a serum-albumin mixture, even when all the β-isoagglutinin acting in saline had been absorbed by the addition of saliva containing B substance; the residual immune agglutinins reached high titers (128 to 2,000 at different temperatures, even in stored specimens) 22 days after delivery, and were still just demonstrable after 161 days; no immune agglutinins against A cells were present,

(*iii*) The indirect Coombs test with B rr cells was still positive after such partial neutralization 22 days and even 161 days after delivery; the corresponding test with A_1 cells was negative,

(*iv*) The thermal optimum for agglutination was shown to be at 37 C. as opposed to the normal 4 to 10 C.; it is interesting that the difference in titer between agglutination at 20 C. and 37 C. was greater in a serum medium than in saline and was still demonstrable in the former after partial neutralization,

(*v*) An anti-B hemolysin was demonstrated.

Unfortunately the diagnosis of hemolytic disease of the newborn was not considered seriously at first as the mother was an Rh-positive primigravida, who had never received any transfusions or injections of blood or serum. Hence the cord blood was not examined, and full investigation of maternal and fetal blood was begun only when the first twin developed signs of kernicterus. The child's blood film contained no immature red cells 7 days after birth, and her serum showed no β-agglutinins at 14 days, but these abnormalities might well have been found earlier. The results of hemoglobin estimations show that during the first three weeks the

anemia was actually more marked in the second infant than in Twin 1, who had jaundice earlier and in whom kernicterus developed.

In determining secretor activity, Smith's[20] technique has been followed except that the cotton-wool swab containing saliva was not soaked in saline; this was thought to avoid an uncertain dilution factor. Equal amounts of saliva from the two twins were expressed from the swabs and tested against grouping sera; the results suggest that secretor activity may be more marked in the second twin, but this must be uncertain.

COMMENT

The clinical findings in these twins, coupled with the positive direct Coombs test six days after birth, indicate that they both had hemolytic disease of the newborn, which led to kernicterus in the first, confirmed at autopsy. When one searches for a cause for this hemolytic disease the evidence points strongly to maternal anti-B antibodies. First, other incompatibilities have been excluded fairly thoroughly. Second, the mother's serum contained β-isoagglutinins to a high titer as well as immune anti-B agglutinins and hemolysins, indicating marked isoimmunization. The positive direct Coombs test shows that the infant's red cells were coated by an antibody; the nature of the latter is not elucidated by the test, but it seems reasonable to assume that it was anti-B antibody as no others were demonstrable in the maternal serum. The best evidence, namely proof of the presence of active anti-B in the children's sera, is not available; yet the diagnosis can be considered as highly probable.

The presence of such a high degree of isoimmunization in a primigravida who has never received injections or transfusions of blood or serum may appear surprising. However, this phenomenon has occasionally been observed by others, not only in pregnant women but also in so-called dangerous universal blood donors (see Ervin and Young[42]). A and B group substance appear to be widespread in the secretions and body fluids of animals, and similar antigens have even been found in bacteria (see Wiener and colleagues,[8b] Mollison[35]). The mother of the twins recorded here had received the usual prophylactic inoculations in the women's services, and the organisms in these vaccines or the culture media on which they were grown, may have contained B substance.[44] Again, she may have become sensitized by infections with certain bacteria.

The clinical findings in the first infant show many points of interest. The absence of hepatosplenomegaly after birth is notable; in Rh incompatibility, the enlargement of liver and spleen, while related to the degree of anemia, has been found to bear no close relationship to the development of kernicterus,[57] and Twin 1, who had little anemia, may also illustrate this point. The first signs of kernicterus were fairly typical. When the critical illness with cerebral irritation and severe jaundice from five to eight days after birth had been overcome, the infant passed into the characteristic latent period.[58] During this stage the chief symptom which caused concern to the parents was the child's excessive crying and screaming "as if in pain," particularly during and after feeds; Perlstein[59] has pointed out that infants having neurological sequelae of erythroblastosis may present as "colic babies."

57. Diamond, L. K.; Vaughan, V. C., III, and Allen, F. H., Jr.: Pediatrics **6**:630, 1950.
58. Evans, P. R., and Polani, P. E.: Quart. J. Med. **19**:129, 1950.
59. Perlstein, M.: Am. J. Dis. Child. **79**:605, 1950.

Increased muscle tone was first noted at 2½ months of age, and choreiform movements were only evident after about 4 months. The latter were of the rapid and jerky type which Evans and Polani [58] consider a particular manifestation of kernicterus. Another interesting feature was the movements of opisthotonic retraction; their diagnostic value was emphasized by Coquet.[60] The lid retraction was associated particularly with downward movement of the eyeballs and may illustrate the "setting sun" sign which is sometimes encountered in these cases.[61]

With regard to the autopsy findings it was to be expected that no evidence of active hemolytic disease would be demonstrable at the age of 9 months. Nor was it surprising to find the brain free from yellow staining, for it has been shown in the past that such staining lasts about three to six months (see Becker and Vogel [62]). The histological abnormalities are in keeping with those found by others after the initial phase of the illness. It is well known that the neuronal damage varies in its extent in different cases, and that not only the basal ganglia and hypothalamic areas may be affected but also the dentate nuclei of the cerebellum, the cornua Ammonis, the olives and cranial nerve nuclei, and various other areas. In hemolytic disease attributed to ABO incompatibility few details of the neuronal lesions have so far been reported. Jervis [10g] recorded the autopsy findings in a girl aged 6 years, in whom kernicterus due to B isoimmunization was diagnosed retrospectively; he found extensive neurocellular degeneration throughout the cerebral cortex and gross damage to the white matter of the hemispheres in addition to the common basal lesions. In the three cases of hemolytic disease due to anti-A reported by Mitchell and colleagues [10d] kernicterus was also extensive but confined to the more usual sites. There is, indeed, no reason to assume that the range of lesions in ABO incompatibility differs from that encountered in kernicterus generally. Damage chiefly confined to the subthalamic body and globus pallidus as in this infant is a familiar finding in the literature, encountered, for instance, in Biemond and Van Creveld's [63] second case and in van Bogaert's [64] patient.

The different severity of the disease in these twins next calls for comment. It is easy to understand that only one of binovular twins may be affected by hemolytic disease, namely, if the other does not possess the agglutinogen against which the mother has produced antibodies. Several such cases have been reported in Rh incompatibility, and Velez Orozco [65] and Boorman and colleagues [10e] met this phenomenon in ABO isoimmunization. However, we are faced with a different problem. The twins recorded here had the same blood group and both suffered from the disease, yet they were affected to a different degree. Such an occurrence has been noted occasionally among Rh cases.[66] The degree of jaundice and anemia may differ considerably in affected twins,[66c] and this may happen even when they

60. Coquet, M.: Ann. pædiat. **163**:83, 1944.

61. Willi, H.: Ann. pædiat. **174**:87, 1950.

62. Becker, P. F. L., and Vogel, P.: J. Neuropath. & Exper. Neurol. **7**:190, 1948.

63. Biemond, A., and Van Creveld, S.: Arch. Dis. Childhood **12**:173, 1937.

64. van Bogaert, L.: Ann. pædiat. **168**:57, 1947.

65. Velez Orozco, A. C.: Blood, Spec. Issue No. 2, p. 164, 1948.

66. (*a*) Buhler, V. B.; Seely, C. W., and McCormick, C.: J. Missouri M. A. **39**:106, 1942. (*b*) Aaberg, M. E., and Roby, C.: Am. J. Obst. & Gynec. **50**:548, 1945. (*c*) Kelly, J. J., and Shaffer, J. G.: J. Pediat. **38**:717, 1951. (*d*) Demy, N. G.: Am. J. Obst. & Gynec. **47**:554, 1944.

are identical.[66d] A similar occurrence in ABO incompatibility was recorded by Robinson and colleagues.[45b] There a group O Rh-positive mothers had Rh-positive binovular twins belonging to group B. Jaundice appeared earlier, and the anemia was more severe, in the first twin, and it is interesting that anti-B agglutinins were found in that child's serum but not in the more mildly affected one. The situation was similar in my patients; a point of difference is that the first twin, who was jaundiced earlier and subsequently developed kernicterus, was actually less anemic than the second during the initial fortnight. It is generally recognized that jaundice and anemia are to some extent independent variables in these cases, as the former may be caused by impaired liver function rather than by hemolysis. Kernicterus occurs almost exclusively in infants with marked jaundice and is not closely related to the degree of anemia.[67]

As twins are exposed to the same original concentration of maternal antibody, any difference in the severity of their disease must be due to an unequal efficiency of their protective mechanisms. The first of these which comes to mind is placental permeability, and this was actually invoked by Demy,[66d] who considered that the portion of placenta serving one twin might have had a greater functional defect than that serving the other, thus resulting in more massive exposure to maternal antibodies. However, there are other possible explanations. The fetal protection against maternal ABO agglutinins was investigated by Tovey,[68] who not only emphasized the lack of placental permeability to those agglutinins but also considered it important that group-specific substances in fetal plasma neutralize A or B antibodies and that the fetal red cells are not as susceptible to agglutination as adult cells. There may have been a difference in the amount of extracorpuscular B substance (possibly indicated by the tests for secretion), or in the sensitivity of the blood or tissue cells to the antibodies, in our twins. Further, as Wiener[69] has suggested, the stage of development of fetal serum proteins may be important in view of their contribution to the so-called conglutination performed by incomplete (or univalent) antibodies, and it may be that twins can differ in the rate of this development; in other words, they may have different amounts of conglutinin in their plasma. Again, the incidence of kernicterus in erythroblastosis is directly related to the degree of immaturity of the infant,[67] and we know that the lesion may even be encountered in premature babies without hemolytic disease.[70] Hence the greater immaturity of the first twin may have contributed to the development of kernicterus. The initial asphyxia may also have played a part.

Unfortunately, in these twins the diagnosis was made too late for any effective treatment to be undertaken. Recently, it has been suggested that the husbands of all group O Rh-positive pregnant women should have their blood group examined so that one may anticipate the occurrence of hemolytic disease due to anti-A or anti-B in the infant.[46] This would seem a wise precaution, although ABO incompatibility does not commonly cause fetal disease severe enough to require treatment. The possibility of the disease should be remembered particularly when an Rh-positive mother has previously given birth to infants affected by erythroblastosis

67. Vaughan, V. C., III; Allen, F. H., Jr., and Diamond, L. K.: Pediatrics **6**:706, 1950.

68. Tovey, G. H.: J. Path. & Bact. **57**:295, 1945.

69. Wiener, A. S.: Am. J. Dis. Child. **71**:14, 1946.

70. Aidin, R.; Corner, B., and Tovey, G.: Lancet **1**:1153, 1950. Zuelzer, W. W., and Mudgett, R. T.: Pediatrics **6**:452, 1950.

or icterus praecox, and perhaps also when there is a history of unexplained abortions (see Waterhouse and Hogben[71]). In suspicious cases A or B substance has often been injected into the infants to neutralize the damaging antibody. In fact, Diamond and his colleagues now use group O Rh-negative blood with these polysaccharides added when giving exchange transfusions for erythroblastosis in Rhesus incompatibility, just in case anti-A or anti-B also play a part in the infant's condition.[72] However, in practice the use of these substances has been disappointing,[14b] and this might be expected as they neutralize immune agglutinins so poorly.[32] Therefore, if a baby is definitely affected by hemolytic disease due to ABO incompatibility the only effective method of treatment is by transfusion. The blood to be used for transfusion should ideally contain group O cells and no α or β agglutinins. Hence washed group O cells suspended in AB plasma serve best,[73] especially for replacement transfusion; A or B substance can be added and the plasma may be diluted with saline to reduce its conglutinin activity.[74] If AB plasma is not readily available, ordinary group O blood (with added A or B substance) may be used, provided the plasma has a low titer of isoagglutinins and contains no immune anti-A or anti-B. For simple transfusion, group O cells suspended in saline should be adequate.

Continental European authors have discussed the problem, familiar from Rh incompatibility, whether breast feeding should be allowed in these cases. It has been shown that the concentration of anti-A agglutinins in the mother's milk may actually be greater than in her serum,[52a] and that milk agglutinins may be absorbed and appear in the infant's bloodstream.[75] It has therefore been suggested that the infant should not be breast fed.[76]

SUMMARY

It is pointed out that incompatibility of the major ABO blood groups between mother and child is gradually being established as an occasional cause of the characteristic forms of hemolytic disease of the newborn, including icterus gravis and even hydrops fetalis. In addition, and more commonly, such incompatibility appears to cause "icterus praecox," a benign condition of early neonatal jaundice, sometimes accompanied by mild anemia and clinically merging into "physiological" jaundice.

The serological diagnosis of neonatal hemolytic disease due to maternal anti-A or anti-B antibodies is discussed in detail. It is emphasized that maternal ABO isoimmunization occurs in a considerable proportion of normal pregnancies without harming the infant. To prove that the clinical and hematological picture of erythroblastosis fetalis is due to anti-A or anti-B it is not sufficient to demonstrate the corresponding ABO incompatibility and an increased titer of α or β agglutinins, or even the presence of immune anti-A or anti-B, in the mother. Other possible

71. Waterhouse, J. A. H., and Hogben, L.: Brit. J. Social Med. **1**:1, 1947.

72. Allen, F. H.; Diamond, L. K., and Vaughan, V. C., III: Am. J. Dis. Child. **80**:779, 1950.

73. Michon, P. and Lochard: Sang **21**:176, 1950. Seigneurin and Groulade.[39e]

74. Seelich, F.; Speiser, P., and Elsner, P.: Wien. klin. Wchnschr. **63**:267, 1951.

75. Masse, L., and Moulinier, J.: Recherches expérimentales concernant le sort des anticorps introduits dans l'estomac des nouveaux-nés par le lait. read before the Fourth International Congress of Blood Transfusion, Lisbon, 1951.

76. Footnotes 52*a*, 54, 39*c*, and 8*d*.

incompatibilities must be excluded thoroughly, and some evidence of the presence, or preferably action, of harmful maternal antibodies in the infant should be provided.

The occurrence of hemolytic disease, probably due to anti-B antibodies, in binovular twins is recorded. Kernicterus ensued in the more immature infant and was verified after death at the age of 9 months. The second twin made a complete recovery without specific treatment.

The clinical features and the investigations, the autopsy findings in the first child, the different severity of the disease in the twins, and the possible treatment of such cases are discussed.

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EXPERIENCES IN TWO HUNDRED EIGHTY-NINE CASES OF INFANTILE DIARRHEA IN A NUTRITIONALLY DEFICIENT GROUP OF INFANTS

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DURING the two-year period of 1950 and 1951, 289 patients with infantile diarrhea were admitted to pediatric department B of the Rambam Government Hospital in Haifa, Israel. All cases of infantile diarrhea which were accompanied by signs of dehydration and acidosis and which called for intravenously administered fluid therapy have been included in this study. We have not included all the milder cases of infantile diarrhea in which no parenterally administered fluid therapy was required and in which the condition improved with the aid of oral administration of fluids only. In other words, this study concerns only cases of infantile diarrhea of a moderate to a severe degree.

We have further confined this study to cases in infants up to 2 years of age, and not above this limit as has sometimes been done by other investigators.

We would here point out that the group of children concerned was remarkable in one very important aspect, namely, that the great majority were grossly deficient in many respects, not only from the point of view of nutrition, and their reactions both to the diarrhea and to its treatment differed from that in an otherwise normal group of children.

We believe a survey of our experiences with this group of children, the methods we employed, and the results we obtained to be of interest in view of these peculiar characteristics.

DESCRIPTION OF MATERIAL

The human material comprising this group is discussed under its two aspects, demographic and clinical.

Demographic Aspects.—Out of the total of 289 patients, 120 were admitted in 1950 and 169 in 1951.

Nearly all of these babies and/or their parents were new immigrants. About 85% had come from Arab or Moslem countries, the Yemen and Iraq heading the list and Morocco, Iran, Tripoli, Egypt, Tunisia, and Turkey following. Only about 15% of the patients originated in European countries. This fact in itself is an indication of the primitive hygienic habits and standards prevailing in these babies' homes.

In this country most of them were living in various types of immigrants' camps. This implies very primitive living quarters, mostly tents and barracks with very rudimentary environmental sanitation. Only a small fraction of the group came to us from better homes in either town or village.

From the Department of Pediatrics, Rambam Government Hospital.

There was no significant difference in incidence between the two sexes.

Chart 1 illustrates the age distribution of the group. The outstanding fact shown by this chart is that the peak incidence in the group was not reached in the first or second month of life as is usually seen in similar statistics,[1] but rather in the fourth month. That this fact is not merely coincidental can be inferred from an analysis of the age distribution of each year separately, as has been done in Chart 2. In this chart the same fact is observed, namely that the peak incidence in each year is reached in the fourth month of life. This observation repeated in two successive years must therefore be of definite statistical significance. Bograchow[2] in this country had already observed this interesting fact previously and ascribed it to

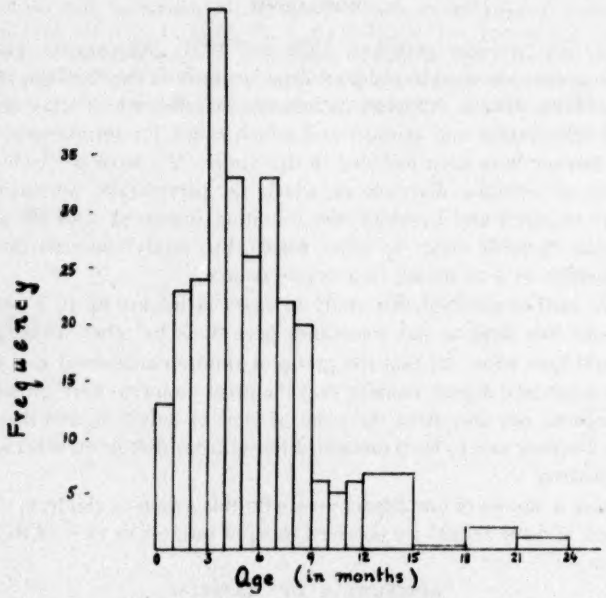

Chart 1.—Age distribution of patients for years 1950 and 1951 combined.

the positive attitude of mothers of Middle Eastern origin to breast feeding. As a matter of fact, nearly every such mother makes a serious attempt at breast feeding, so that during the first few months of its life the infant is usually not fed contaminated milk. However, because of the poor nutritional status of most of these mothers, their milk supply is insufficient, so that malnutrition develops in their babies from starvation at an early stage. To correct or to prevent this state supplementary feeding is started by these mothers at an early age with the result that contaminated food consumption becomes possible, and the wave of diarrheas rises rapidly, reaching its maximum in the fourth month.

1. Flett, J. Jr.; Pratt, E. L., and Darrow, D. C.: Methods Used in the Treatment of Diarrhea with Potassium and Sodium Salts, Pediatrics **4**:604-619, 1949. Smellie, J. M.: Infantile Diarrhœa (Ingleby Lecture), Lancet **1**:969, 1939.

2. Bograchow, N.: Infantile Diarrhœa in Tel-Aviv During the Years 1938-1940, Harefuah **21**:35-40, 1941.

Chart 3 illustrates the monthly incidence in our series, and here again another important fact may be observed. In contrast to most statistics in which a definite 20- to 30-fold peak is usually seen during some months of the year, no such feature was observed in our series. On the contrary, the ratio between the highest and the

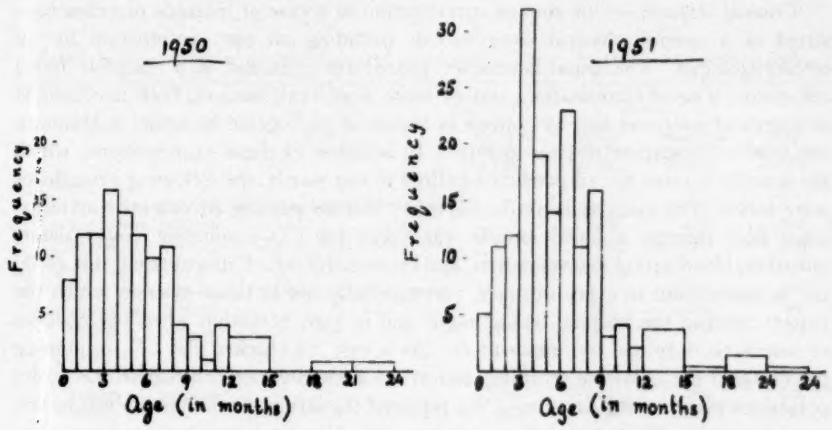

Chart 2.—Age distribution of patients for years 1950 and 1951 separately.

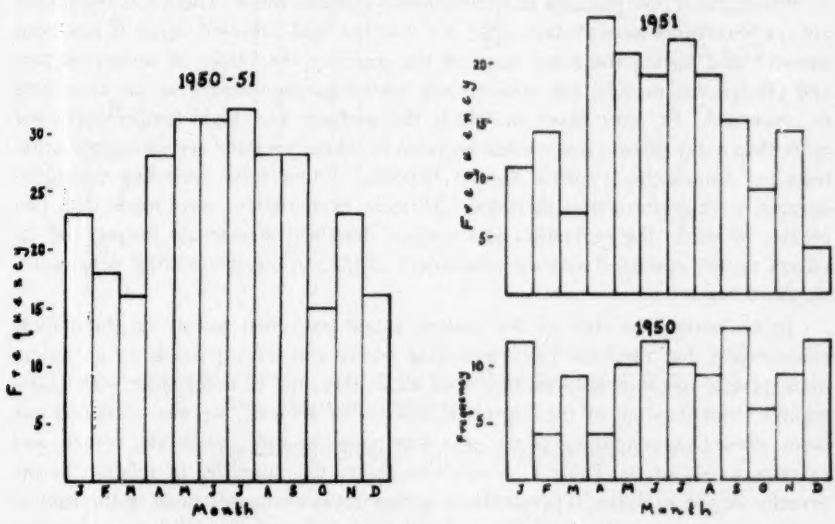

Chart 3.—Monthly incidence of disease.

lowest monthly incidence in our series as seen in the chart is only around two to one. Furthermore, the peak in most statistics is reached during some summer month, usually August. This is also the case in our series when considered as a whole with the peak in July. When split up, however, into the separate years under consideration, it is seen that the peak incidence in 1950 occurred in September,

while in 1951 it occurred in April. A possible explanation for these facts may be found in the very low sanitary conditions prevailing all the year round, which in themselves are enough to provide a steady flow of cases of infantile diarrhea. The summer heat is thus not an essential prerequisite for a seasonal increase in the number of cases.

Clinical Aspects.—Our routine investigation of a case of infantile diarrhea consisted of a careful physical examination, including an ear examination by an otolaryngologist. The usual laboratory procedures consisted of a complete blood cell count; a urine examination; one or more stool examinations, both microscopic in search of protozoa and by culture in search of pathogenic bacteria; a Mantoux test, and a Rappaport test for syphilis. In addition to these examinations, which are actually routine for all patients admitted to our wards, the following procedures were followed in cases of infantile diarrhea: Before starting parenterally administered fluid therapy a blood sample was taken for CO_2-combining power determination, blood-group determination, and cross-matching. Unfortunately this could not be carried out in every instance, and especially not in those cases in which the patient reached the hospital late at night and in poor condition when the resident or intern on duty had too much to do. As a rule we checked the CO_2-combining power again the following morning, and at the same time we determined the serum potassium value for the first time. We repeated the serum potassium determinations once or twice until normal values were reached. In a large proportion of our cases we also determined the serum calcium, phosphorus, and alkaline phosphatase values as well as the serum proteins and the albumin-globulin ratio. These last tests were always performed several days after the diarrhea had subsided, since it has been shown [3] that during the acute stage of the diarrhea the values of serum calcium and phosphorus may be low without any pathologic significance as far as rickets is concerned. In most cases in which the patients had high temperatures for more than a day or two, our routine included blood cultures and serum agglutination tests for Salmonella, Proteus X, and Brucella. Other tests, including roentgenograms, were performed as indicated. All these examinations were made with two objects in mind: the evaluation of the acute diarrheal disease, its causes, and its effects on the one hand and the assessment of the various preexisting deficiencies on the other.

In evaluating the state of the acidotic infant we relied mainly on the clinical examination, but used the CO_2-combining power whenever possible as an aid in more precise intravenously administered alkali therapy. In accordance with Hartmann's [4] classification of the degree of severity of acidosis, we also classified our cases when CO_2-combining power was determined as mild, moderate, severe, and extreme as shown in Table 1, which also shows the mortality in relation to the severity of the acidosis. The outstanding fact revealed in this table is the lack of relationship between the mortality and the degree of acidosis. With the exception

3. Rapoport, S.; Dodd, K.; Clark, M., and Syllm, I.: Postacidotic State of Infantile Diarrhea—Symptoms and Chemical Data: Postacidotic Hypocalcemia and Associated Decreases in Levels of Potassium, Phosphorus and Phosphatase in Plasma, A. M. A. Am. J. Dis. Child. **73**:391-441, 1947.

4. Hartmann, A. F.: Round Table Discussion: Acidosis and Alkalosis, Pediatrics **2**:584-608, 1948.

of the mild cases, the mortality rate is practically the same for the various groups. This again is, in our opinion, an expression of the type of patient of which this group was composed. The degree of severity of the acidosis was not the most important factor in determining the outcome of the illness. The general condition of undernutrition and deficiency was of greater importance in determining the final outcome.

TABLE 1.—*Classification of Diarrheas and of Mortality Rates According to Severity Index*

	Degree			
	Extreme (5-15 Vol. % CO_2)	Severe (15-25 Vol. % CO_2)	Moderate (25-35 Vol. % CO_2)	Mild (35-45 Vol. % CO_2)
1950				
Of 75 cases with CO_2-combining power determined..	..	17	37	21
Percentage incidence	..	23%	49%	28%
Deaths	..	24%	24%	14%
1951				
Of 86 cases with CO_2-combining power determined.	5	25	35	21
Percentage incidence	6%	29%	41%	24%
Deaths	20%	28%	17%	5%
1950-51				
Of 161 cases with CO_2-combining power determined	5	42	72	42
Percentage incidence	3%	26%	45%	26%
Deaths	20%	26%	21%	10%

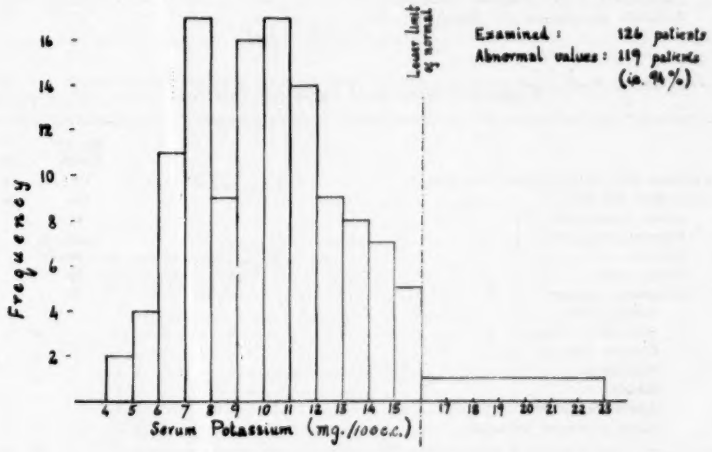

Chart 4.—Distribution of the degree of hypokalemia.

In a significant number of cases we encountered the clinical symptoms of hypokalemia, namely, listlessness, diminished muscle tone, meteorismus, and sudden cessation of diarrhea. These symptoms usually appeared after the state of dehydration had been corrected by intravenously administered fluid therapy. The appearance of such symptoms, however, did not always correspond to the degree of chemical hypokalemia as revealed by the serum potassium determinations. At times very low serum potassium values were encountered without any clinical signs of hypokalemia, while in other cases moderately low serum potassium values were

often associated with distinct clinical manifestations. Unfortunately we were not in a position, because of technical difficulties, to make use of the electrocardiogram in evaluating the frequency and degree of hypokalemia. The serum potassium values were determined in 126 cases, and in 119 (i. e., 94%) low values were found. Chart 4 shows the distribution of the degree of hypokalemia.

The stool examinations disclosed pathogenic organisms of the Shigella and Salmonella groups in 4.5% of our cases only. Giardia lamblia was found in 8%, and in 36% of our cases various micro-organisms were found as shown in Table 2.

TABLE 2.—*Incidence of Enteric Organisms*

Organism Isolated	Cases	%
Protozoa		
Giardia lamblia	22	8.0
Trichomonas hominis	4	1.5
Bacteria		
Shigella flexneri I	6	4.5
Shigella sonnei	2	
Salmonella paratyphi B (Schottmuller)	2	
Salmonella paratyphi C (Newport)	2	
Proteus morgagnii	43	33
Proteus mirabilis	8	
Proteus rettgeri	1	
Providence group (anaerogenic strains of Paracolobactrum)	21	
Bethesda group (Paracolobactrum intermedium)	2	
Alkalescence group (Shigella alkalescens)	2	
Klebsiella pneumoniae (B. friedlander)	19	

TABLE 3.—*Incidence of Parenteral Infection*

	No. of Cases	%
Diarrhea without parenteral infection	135	47
Parenteral diarrhea	154	53
Acute pharyngitis	81	
Bronchopneumonia	47	
Pyuria	32	
Otitis media	30	
Infectious diseases	21	
Poliomyelitis	7	
Whooping cough	6	
Chicken pox	3	
Diphtheria	2	
Measles	1	
Acute aseptic meningitis	1	
Acute infectious hepatitis	1	

With the exception of Shigella and Salmonella, we were never convinced of the pathogenicity of these various bacteria. On the one hand, the finding of one or another of these organisms in the stool was very often unrelated to the presence or absence of diarrhea. On the other hand, we never noticed any difference between the severity of the diarrhea in children from whose stool some agent of the above was isolated and that in children from whose stool none was cultured.

The important role played by parenteral infection in relation to diarrhea in our series is illustrated in Table 3. Only 47% of our patients had no discoverable focus of infection, whereas the remaining 53% showed one or more such foci.

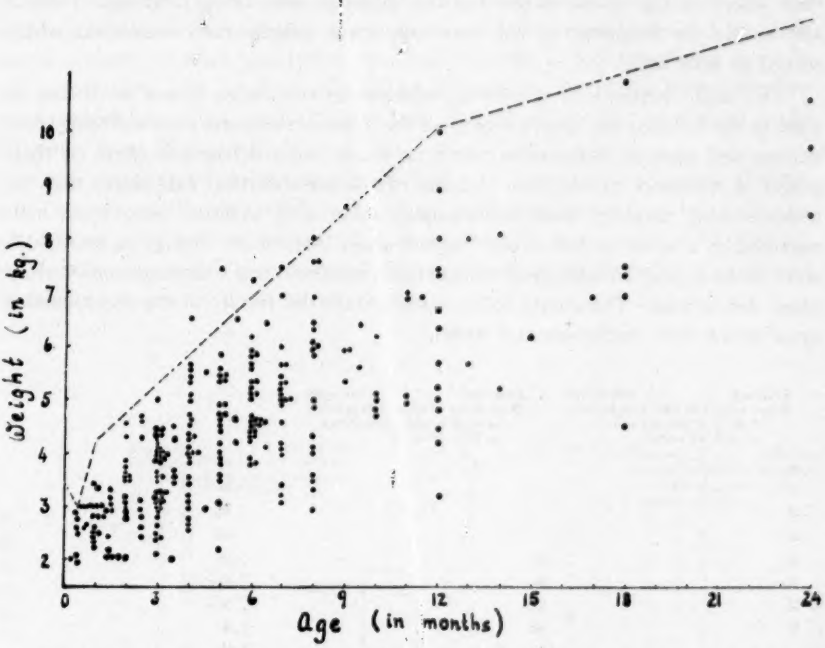

Chart 5.—Spot diagram showing weights for respective ages of the infants as compared with the optimal weight curve.

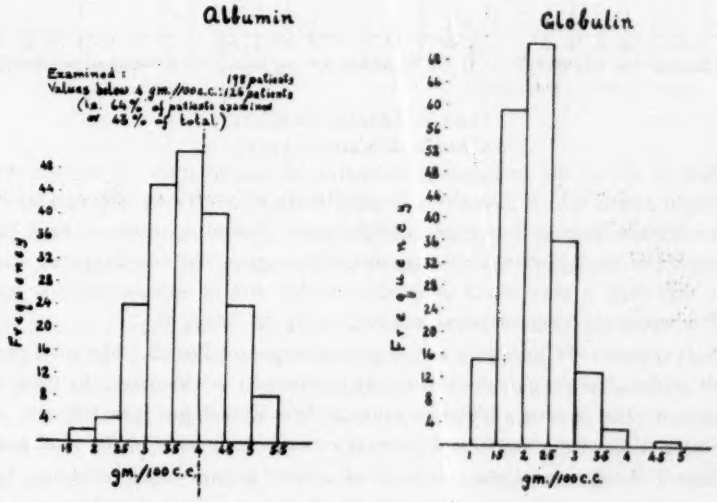

Chart 6.—Incidence and degree of hypoproteinemia.

their effect on the course of the diarrhea in many cases being clear-cut. Table 3 also shows the frequency of the most important inflammatory conditions which served as such foci.

This high incidence of parenteral infection in our series is not surprising in view of the fact that the large majority of the infants concerned were suffering from various and multiple deficiencies which no doubt had a deleterious effect on their power of resistance to infection. An analysis of our statistical data shows that the overwhelming majority were underweight, about 50% suffered from frank malnutrition to a more or less severe degree, about 40% were anemic, at least 30% were rachitic, and an additional considerable number were suffering from various other deficiencies. The charts following illustrate the results of the examinations upon which our conclusions are based.

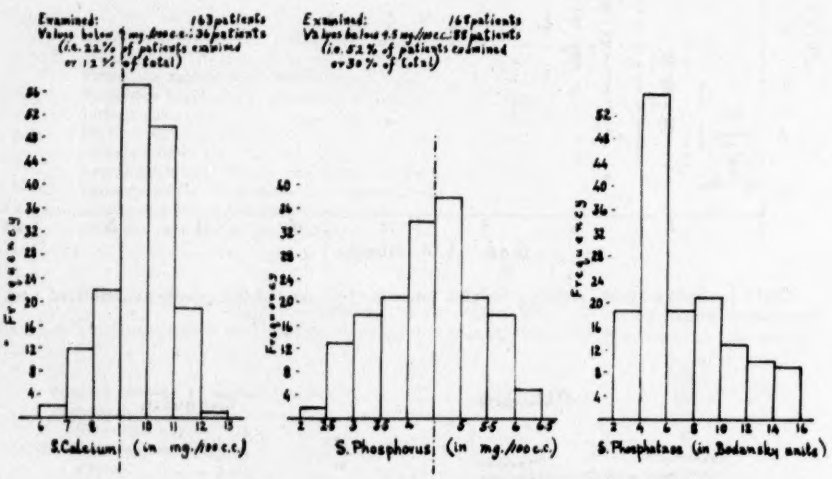

Chart 7.—Incidence of rickets.

Chart 5 shows the incidence and degree of malnutrition. Upon an average age-weight chart, which is commonly used in this country by the various child-welfare centers, having the optimal weight curve drawn upon it, we have plotted the weights of the infants against their respective ages. The resulting spot diagram shows that only a very small proportion of our babies approached this optimal curve, whereas the overwhelming majority were far below it.

Chart 6 shows the incidence and degree of hypoproteinemia. The total proteins as well as the albumin-globulin ratio were determined in 198 cases. In these cases, 126 patients had a serum albumin value of less than 4 gm. per 100 ml., which constitutes 64% of the number of patients examined, or 43% of the total number.

Chart 7 demonstrates the incidence of rickets in our series as shown by the biochemical values of their serum calcium, phosphorus, and phosphatase. Out of a total of 168 patients examined for serum phosphorus, 88 patients were discovered to have a value of less than 4.5 mg. per 100 ml., which is the lower limit of normal

in our age group. This number constitutes 55% of those examined, or 30% of the total number of patients. Again, out of a total of 163 patients examined for their serum calcium, 36 were found to have a calcium value of less than 9 mg. per 100 ml., constituting 12% of the total number of patients. As to the serum alkaline phosphatase, the values obtained were such that no diagnostic conclusions could be drawn from them.

Chart 8 illustrates the incidence and degree of anemia in our series. Thirty-seven per cent of the total number of patients had hemoglobin values below 10 gm. per 100 ml., and 50% of the total had an erythrocyte count below 4,000,000 per cubic millimeter, values that are generally considered as the lower limits of normal in the age group with which we are dealing.

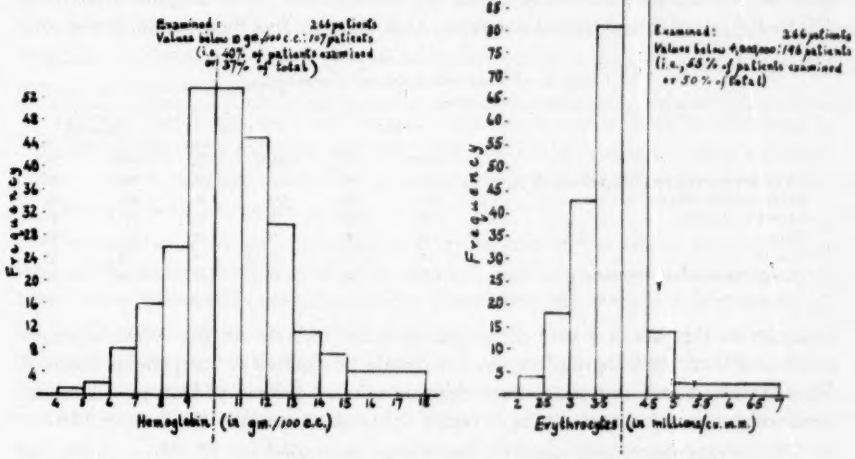

Chart 8.—Incidence and degree of anemia.

THERAPY

The treatment administered to these infants could be advantageously discussed under three headings: intravenous fluid therapy, dietetic therapy, and antibacterial therapy.

Intravenous Fluid Therapy.—In our service rehydration was carried out through one of the ankle or elbow veins generally entered after a "cut-down," and the fluids were administered by a slow continuous drip infusion. We usually started with a 5% dextrose solution in half isotonic sodium chloride solution, into which molar sodium lactate, applied in 10 cc. ampules, is added in an amount sufficient to correct the acidosis, as calculated from the CO_2-combining power deficit determined in the laboratory. In those cases in which the CO_2-combining power could not be determined because of technical difficulties, such as when the baby was admitted in the middle of the night, molar sodium lactate solution was added at the rate of

5 cc. per kilogram of body weight in mild acidosis, 10 cc. per kilogram in moderate, and 15 cc. per kilogram in severe acidosis, based on our clinical evaluation of the case. This first solution in amounts of 50 to 60 cc. per kilogram of body weight was run in quickly through the drip as fast as it would flow when wide open.

This first solution was followed in a considerable number of cases, and in particular in the severer ones, by a blood transfusion in amounts of 20 cc. per kilogram of body weight. We sometimes administered plasma instead of blood. The object of these fluids was to counteract the state of shock frequently accompanying the acidosis and to supply the body with additional base in the form of sodium citrate contained in stored blood.

After this we proceeded with the administration of thin fluids in the form of diluted Darrow's solution. Our hospital is supplied with concentrated Darrow's solution in 10 cc. ampules which when dissolved in 178 cc. of distilled water results in the original Darrow's solution. Since Darrow [5] recommends, for intravenous purposes, to dilute his original solution two- or three-fold with 5% dextrose solution, we attained this same object by diluting our 10 cc. ampule directly in 350 to 400 cc. of 5% dextrose solution. This solution was then administered con-

TABLE 4.—*Fluids Administered Parenterally*

	1950		1951		1950-1951	
	Cases	%	Cases	%	Cases	%
5% dextrose in ½ isotonic sodium chloride	120	100	169	130	289	100
Molar sodium lactate	110	92	154	91	264	91
Darrow's solution	19	16	98	58	117	40
Blood	44	37	73	43	117	40
Plasma	37	31	16	9	53	18
Protein hydrolysate (Amigen)	36	30	19	11	54	19

tinuously at the rate of 2 to 3 drops per kilogram of body weight, which amounts to about 200 cc. per kilogram per day. A certain proportion of our patients received 5% dextrose in half isotonic sodium chloride solution instead of Darrow's solution, while others received both kinds of fluids. This was especially the case in 1950.

The intravenously administered fluids were continued for 12, 24 or, rarely, 48 hours, and their administration was stopped as soon as we were convinced that the dehydration and acidosis were completely repaired and as soon as the baby could tolerate fluids orally without vomiting. We practically never continued with the same "cut-down" for more than 48 hours for fear of thrombophlebitis. If the condition of the baby called for intravenously administered fluids for more than 48 hours, we usually performed another "cut-down."

This is the general routine of intravenously administered fluid therapy as practiced in our service, although it was not always strictly adhered to in view of the fact that certain details were laid down in the course of this two-year period.

Table 4 illustrates the types of fluids used and the frequency of use. Less plasma and protein hydrolysate (Amigen) was used in 1951 than in 1950 because these fluids were in short supply.

5. Darrow, D. C., and Pratt, E. L.: Fluid Therapy: Relation to Tissue Composition and Expenditure of Water and Electrolyte, Council on Foods and Nutrition, J. A. M. A. **143**:365-373, 1950, and **143**:432-439, 1950.

Dietetic Therapy.—We generally allowed an initial starvation period of 8 to 12 hours only, during which time the baby received fluid by vein only. Following this period, and while the baby was still receiving fluids by vein, oral feeding was started in small amounts with a rapid increase to full amounts in about 4 to 5 days. After interrupting the intravenous administration of fluids, we completed the babies' daily fluid requirements by giving Ringer's solution diluted to one-third of its concentration orally.

The initial starvation period was very rarely prolonged to 24 hours and practically never beyond that. Our sole criterion for starting oral feeding was the presence or absence of vomiting and not the intensity of the diarrhea. When the baby stopped vomiting, which was the rule after the states of dehydration and acidosis had been counteracted, we had no hesitation in starting and then increasing oral feeding rapidly to the amounts the baby was prepared to take, without bothering about the state of the diarrhea. We experienced no difficulties in employing the early oral-feeding method, although we did not apply it as strictly as advocated by Chung and Viscorova [6] and others.[7] However, we are convinced of its advantages, especially in the malnourished type of infant for whom prolonged starvation could indeed be very detrimental.

The first food employed after the initial starvation was buttermilk (Eledon) in 60%. In another 30% half milk was employed, and in the remainder either skimmed milk or protein milk was used. We found buttermilk preferable in infantile diarrhea, as compared with the other milks.

Antibacterial Therapy.—Practically every patient in our series received some kind of chemotherapeutic agent. Our general routine consisted of starting most babies on a sulfonamide preparation first (this being the cheapest) in a dosage of 0.1 to 0.2 gm. per kilogram of body weight per day. If the diarrhea showed signs of improvement on this therapy within two or three days we continued use of the sulfonamide preparation for 7 to 8 days. Otherwise we stopped using this preparation and started oral administration of 0.5 gm. of streptomycin daily given in four equal doses. Here again, if the diarrhea showed signs of improvement within two or three days, we continued this therapy for a total of 7 to 8 days, but if not, we stopped use of streptomycin and started giving the baby 50 mg. of aureomycin per kilogram of body weight per day. We rarely skipped the sulfonamides, and in exceptional cases only started with aureomycin right away. We had to employ this routine because of the necessity of economizing on aureomycin, the supply of which was limited.

The sulfonamide preparations we employed were sulfaguanidine in 116 cases, sulfadiazine in 91 cases, and sulfasuxidine in 13 cases. In 16 cases chloramphenicol (Chloromycetin) was employed in addition to the other agents when aureomycin also had no effect on the diarrhea.

6. Chung, A. W., and Viscorova, B.: The Effect of Early Oral Feeding Versus Early Oral Starvation on the Course of Infantile Diarrhea, J. Pediat. **33**:14-22, 1948.

7. Mitchell, J. E.; Donald, W. D., and Birdsong, M.: A Review of 396 Cases of Acute Diarrhea in Which Early Oral Feedings Were Employed in Treatment, J. Pediat. **35**:529-539, 1949.

In addition to these agents, penicillin was administered parenterally in 60% of our cases, either as the treatment of some parenteral infection or as the treatment of a thrombophlebitis which developed in some cases as a result of the "cut-down," or in others as a preventive of this complication.

In the eight cases the patients received quinacrine (Atabrine) therapy against giardiasis with only one favorable result. Mention may be made here of potassium chloride, which was administered orally in 12% of the cases in 1950, and to 42% of the patients in 1951.

TABLE 5.—*Drug Effectiveness*

	Total No. Cases	Good Effect		Doubtful Effect		No Effect	
		Cases	%	Cases	%	Cases	%
Sulfaguanidine	116	20	17	18	15.5	78	67.5
Sulfadiazine	91	15	16.5	9	10	67	73.5
Streptomycin (orally)	121	25	21	21	17	75	62
Aureomycin	83	26	31	12	14.5	45	54.5
Chloramphenicol (Chloromycetin)	16	2	12.5	2	12.5	12	75

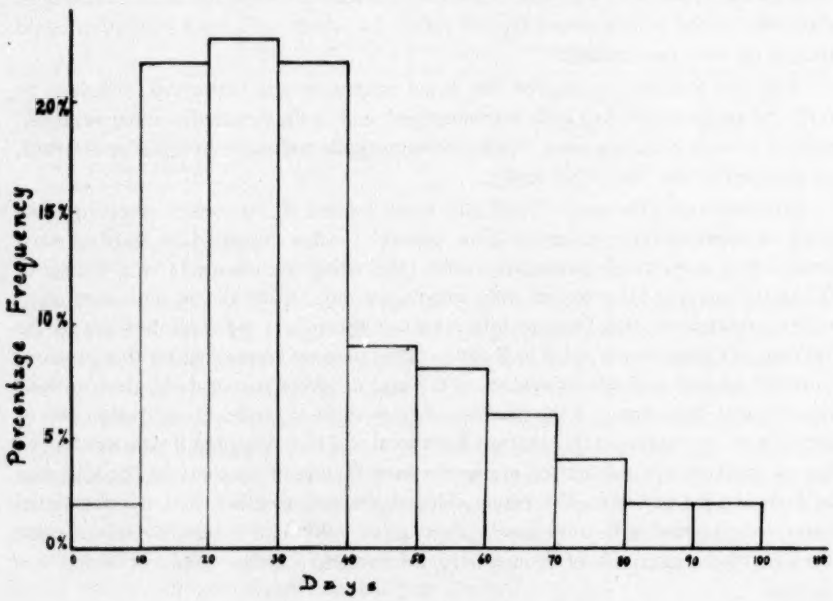

Chart 9.—Length of hospital stay.

Table 5 illustrates the results of therapy with the various antibacterial agents. We considered the effect of therapy "good" when the diarrhea stopped entirely within 2 to 3 days, "doubtful" when the diarrhea stopped within 5 to 6 days, and "none" when there was no change in the diarrhea. Table 5 shows the high percentage of failures with whatever therapy employed. It is our impression that whatever good effect antibacterial therapy may have on a diarrheal state such effect is indirect, the direct effect being on the parenteral focus of infection apparent or undetected.

RESULTS

Out of the 289 infants admitted to the service 231 recovered and 58 died.

The fact that the large majority of these babies were nutritionally deficient in many respects had its bearing on those who recovered as well as on those who died. This expressed itself in the length of the hospital stay on the one hand and in the mortality rate on the other.

Length of Hospital Stay.—Of those who recovered less than half were discharged within the first month of admission, while the rest remained in the service for two and even three months, and a few remained even longer, as shown in Chart 9. That this unusually prolonged period in the hospital was not due to the diarrhea itself is shown by the fact that in 61% the diarrhea stopped within the first 10 days, in 82% it stopped within the first 20 days, and in only less than 7% it continued beyond the first month, as compared with over 50% who remained in the service that long. On the other hand, 37 infants, constituting about 13% of total admissions, had relapses during their hospital stay, requiring renewed intravenously administered fluid therapy. Most of these relapses occurred during the third and fourth week of their hospital stay, but 6 out of the 37 had another relapse about two weeks after their first relapse. The various nutritional deficiencies no doubt had a deleterious effect upon the length of the period of diarrhea and upon the relapse rate as well as upon the frequency and severity of parenteral infections and infectious complications. All these factors had their effect on the length of the hospital stay, but, in addition, the nutritional deficiencies in themselves constituted the direct and main cause for the excessive prolongation of the hospital stay in about 60% of our patients.

TABLE 6.—*Mortality Rate*

	1950		1951		1950-1951	
	Cases	%	Cases	%	Cases	%
Over-all mortality	30	25	28	17.5	58	20
Deaths due to causes other than toxicosis	8	7	11	6.5	19	6.5
Deaths within 24 hours of admission	7	6	6	3.5	13	4.5
Corrected mortality	15	12	11	6.5	26	9

Mortality.—The mortality rate in our service is shown in Table 6. The over-all mortality for the two-year period was 20% with a corrected mortality of 9%.

We pointed out previously the lack of relationship in our group between the mortality rate and the severity index, and this was accounted for by the type of human material that composed our series. This same fact easily accounts for the rather high mortality rate in our series as compared with most modern series. It also accounts for the difference in mortality rate between the two years separately, since the deficiencies of the infants admitted in 1950 were severer than those of the infants admitted in 1951. Thus, while in 1950 the corrected mortality rate was 12%, it was only 6.5% in 1951.

SUMMARY

A study of 289 cases of infantile diarrhea in a severely malnourished group of infants has been presented. The methods of examination and treatment have been outlined and the results obtained evaluated. The effect of the nutritional deficiencies on the course and outcome of the disease has been stressed.

CLINICAL STUDY OF SKIN RASHES DURING THE NEWBORN PERIOD

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PHILADELPHIA

THAT THERE has been a great deal of interest in recent years in the problem of the prevention and treatment of the various types of rashes which appear in newborn infants is amply attested to by the number of articles appearing in the pediatric journals during the past 30 years discussing the effectiveness of this or that preparation in this field.

In a clinical study of various methods used for the prevention of impetigo neonatorum published in 1944,[1] the literature to that date was reviewed and a study made over a seven-year period of the results with three separate methods of skin care, i. e., (1) sterilized cottonseed oil, (2) the "no bath technique" as originally recommended by Bean and Smith in 1936, and (3) the "no bath technique" plus the use of a lotion containing a quaternary antiseptic, with an apparent advantage to the third method.

Since that time there have been five additional reports of a similar nature on the apparent effectiveness of various preparations in the prevention of impetigo neonatorum: one emphasizing the value of the "no bath technique" alone[2]; two, the use of a 5% sulfathiazole ointment[3]; a fourth, the use of lotions containing 8-hydroxyquinoline as their antiseptic agent,[4] and the other,[5] hexachlorophene in a lotion base.

The majority of articles appearing since 1944 have been concerned primarily with the problem of ammonia dermatitis of the diaper region—a problem rarely encountered until later in infancy. Here we find reports of a series showing the

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Presented before the Philadelphia Pediatric Society, Nov. 11, 1952.

From the Divisions of Pediatrics and Obstetrics of the Hahnemann Medical College and Hospital of Philadelphia.

1. Fischer, C. C.: Prevention of Impetigo Neonatorum: A Clinical Study of Various Methods Including Use of New Antiseptic Baby Lotion, Arch. Pediat. **61**:352-357, 1944.

2. Apfel, H.: A Simplified Method of the Care of the Skin of the Newborn, Arch. Pediat. **66**:131-134, 1949.

3. (*a*) Weymuller, C. A., and Ittner, E. J.: Sulfathiazole Ointment for Prevention and Treatment of Pyodermas of Newborn Infants: Results Obtained with 5 Per Cent Sulfathiazole in an Oil in Water Type Emulsion Base, Am. J. Dis. Child. **69**:283-286, 1945. (*b*) Lee, H. F.; Wilson, R. B.; Brown, C. E., and Reed, T. P.: Impetigo and Acute Infectious Exfoliative Dermatitis of the Newborn Infant (Ritter's Disease), J. Pediat. **41**:159-169, 1952.

4. Perlstein, M. A.: Evaluation of Certain Preparations for Care of the Skin of Newborn Infants, Am. J. Dis. Child. **75**:385-394, 1948.

5. Niedelman, M. L., and Bleier, A.: Ammonia Dermatitis: Treatment with Diaperene Chloride Ointment, J. Pediat. **37**:762-764, 1950.

value of such preparations as the quaternary antiseptics,[6] either as diaper rinses, ointments, or powders; of a synthetic chlorophenol as a diaper rinse,[7] and of methionine administered orally.[7a]

Of considerable interest is the fact that not only do these articles attest to continued attention to this problem, but also to a rather startling lack of unanimity as to the method of skin care of greatest value.

This lack of unanimity was further brought out in a recent survey of 83 large hospitals on "Current Practices in the Care of the Newborn."[8] In this so-far unpublished report, it was noticed that in reply to the question concerning the initial bath, 5 hospitals reported no bath; 3, bath only after 12 hours; 20, that the entire body was cleansed; 22, a shampoo plus the entire body bath, and 4, the removal only of obvious soil. In reply to the question concerning the solutions used on the skin for this initial bath, 20 hospitals reported the use of oil; 16, soap and water alone, and 3, soap and water followed by oil. Eleven used water alone; 2, water followed by oil; 5, lotion; 6, dry technique, and 20, a substance not specified.

In reply to the query concerning the material used for a daily cleansing after the initial bath, 35 reported the use of plain water; 24, the use of oil; 18, the use of soap and water; 10, the use of lotions, and the others used various preparations such as alcohol, alcohol or oil, boric acid, cetyl pyridinium (Ceepryn) chloride 1:1,000 dilution, penicillin ointment, pHisoderm (4), benzalkonium (Zephiran) (2), and only 1, the dry technique.

This marked variety of methods of skin care is particularly interesting when one notes that in "The Standards and Recommendations for Hospital Care of Newborn Infants"[9] published by the Committee on Fetus and Newborn of the American Academy of Pediatrics we find under the item, "Care of the Skin,"

> The proper care of the skin in the newborn infant is important in preventing infection. At present the consensus of opinion seems to be that the less manipulation, the less danger of infection. It is recommended that no water or oil bath be given during the first week or ten days after birth. The buttocks may be gently wiped away from the folds of the infant's skin with warm sterile mineral oil on sterile cotton or soft sterile gauze. Each time the diaper is changed, sterile oil should be applied to the soiled or wet areas of the skin.

A disparity between this authoritative opinion and the results of the questionnaire prompted the author of the questionnaire to state, "no study could be found in the

6. Benson, R. A.; Slobody, L. B.; Lillick, L.; Maffia, A., and Sullivan, N.: A New Treatment for Diaper Rash: Preliminary Report, J. Pediat. **31**:369-374, 1947. Benson, R. A.; Slobody, L. B.; Lillick, L.; Maffia, A., and Sullivan, N.: The Treatment of Ammonia Dermatitis with Diaparene, ibid. **34**:49-51, 1949. Pfeffer, W., Jr., and Smith, C. A.: A Note on the Treatment of Diaper Rash with Alkyl-Dimethyl-Benzyl-Ammonium Chlorides (Roccal), ibid. **37**: 351-356, 1950. Niedelman and Bleier.[5]

7. Stephens, L. J.; Cook, V. M., and Heberling, A. M.: o-Benzyl-p-Chlorophenol in the Prevention and Treatment of Ammonia Dermatitis, J. Pediat. **40**:750-756, 1952.

7a. Goldstein, L. S.: Napkin Dermatitis Caused by Ammoniacal Urine: Treatment with Methionine, Arch. Pediat. **66**:553-560, 1949.

8. Latham, H. C., R.N.: Current Practices in the Care of the Newborn: Survey of 83 Hospitals: Unpublished report, August 1951.

9. Standards and Recommendations for Hospital Care of Newborn Infants, Full-Term and Premature: Committee on Fetus and Newborn, The American Academy of Pediatrics, New York, Borden Company, 1949.

literature on the use of water on the skin or comparison of values of using water or a lotion on the baby's skin." She also came to the following general conclusions: (1) Practices vary widely in the care of the newborn; (2) many practices are not in accord with the recommendations set up by the Committee on Fetus and Newborn of the American Academy of Pediatrics, and (3) there is need for scientific knowledge and development of criteria on which to judge certain techniques and practices, for there is an unfortunate meagerness in available literature by nurses on nursing techniques in the nursery.

In the field of comparative studies we note that in addition to the one of the relative incidence of impetigo under three different methods previously alluded to,[1] only those of Weymuller and Ittner,[3a] Perlstein,[4] Glaser,[10] and Heimer and co-workers [11] attempted to compare statistically the effect of various methods.

The first of these [3a] compared the incidence of impetigo in consecutive series employing isolation only (1.3%), inunction with 2% ammoniated mercury ointment (1.2%), and inunction with 5% sulfathiazole ointment, with the latter showing the lowest incidence (0.2%).

The second report [4] similarly compared consecutive series of cases in which ammoniated mercury rubs and various lotions (with and without 8-hydroxyquinoline as an antiseptic) were used, with special reference to the number of infants showing miliaria, and, secondarily, other rashes. It was concluded that the water in oil emulsions or lotions was the most effective and that the added antiseptic, although not shown to be an irritant, is not the important factor in the prevention of miliaria or impetigo. Reference was made to the seasonal incidence of miliaria as a factor in that and other rashes, and the percentages of incidence of miliaria varied from 30.0% in the oil group to 10% in the lotion-treated group.

The third report [10] also compared consecutive series. This time a group treated with a 5% sulfathiazole ointment was used as the control with two other groups being treated by a general inunction with a lotion containing 1% hexachlorophene after an initial soap-and-water bath followed by daily soap-and-water baths thereafter, with the lotion used only in the diaper area after each diaper change on these days. The only difference between the second and third groups was that with one an acid type of lotion was used and with the other an alkaline one. The latter was found to be slightly superior to the former, and the incidence of miliaria and impetigo (1.9% and 0.19%) to be comparable to the incidence in the sulfathiazole-treated control group, without the dangers of sensitization.

The final comparative study [11] was done by treating alternate newborn infants with local application of sterile mineral oil and a cod-liver-oil ointment. Here there was found to be an incidence rate of 1.35% of rashes in the mineral oil group and 0.85% in the cod-liver-oil ointment group, of which approximately one-half were pustular rashes.

An analysis of these few published comparative studies immediately reveals the impossibility of satisfactorily comparing any one series with another and, in

10. Glaser, J.; Thompson, M. L., and Benson, T. D.: Prevention of Minor Skin Irritation (Miliaria) and Impetigo in the Newborn, A. M. A. Am. J. Dis. Child. **81**:329-334, 1951.

11. Heimer, C. B.; Grayzel, H. G., and Kramer, B.: Local Therapy in Dermatoses of the Newborn Infant, Arch. Pediat. **68**:382-387, 1951.

several instances, of adequately interpreting the results of even a single study with such obvious variables as the season of the year, differences in appraisal of the nature of a rash by different observers, and the fallacy of comparing consecutive rather than simultaneous series.

Feeling that there was a real need for a careful estimation of the incidence of the various rashes met with in the newborn period as well as a controlled study of the apparent effect of various skin applications upon this incidence, we decided to attempt such a study more than a year ago.

METHOD OF STUDY

Having felt, as a result of our previous experience, that the lotions containing quaternary antiseptics gave satisfactory results, we decided first to compare the results with two different lotions. Lotion A [12] was the lotion used in our earlier study, except that present lots contain as the active antiseptic cetyl pyridinium chloride instead of the cetyl trimethyl ammonium bromide formerly used, and is an oil-and-water emulsion. Lotion B [13] similarly contains another one of the quaternary antiseptics, (methylbenzethonium chloride), but differs from Lotion A in that it is in a base made up of cholesterol and related sterols.

In order to eliminate as far as possible such variables as season of the year and individual differences of appraisal, the nurseries were divided into two groups, one the private nursery and the other the ward and premature nurseries together, each group using the same lotion for three consecutive months under the supervision of the same nurses and then the lotions being reversed in usage for the next three months. This process was repeated twice more for a period of one year in all.

A modification of the "no bath technique" was employed. No soap-and-water baths were given these infants, only the excessive soil being carefully removed with the lotion on cotton shortly after birth and the respective lotions then being applied once daily to the entire body, and as needed locally after each diaper change.

Each supervising nurse was required to report weekly the incidence of rashes in her group and to call all such rashes to the attention of the house staff for confirmation. It was originally decided to divide all rashes into the categories of pustular rashes, inflamed buttocks, intertrigo, miliaria, and others. Experience soon revealed that in this age group (under one week for all but the premature infants) intertrigo was an insignificant factor statistically, and that the only type of rash reported under "others" was an excessively dry skin, with or without peeling. The categories of pustular rashes, inflamed buttocks, miliaria, and dry skin were then selected as the ones to be used for a comparative study.

After the full year of study, during which more than 3,000 infants were so observed, it was felt advisable to try two small but statistically significant control groups, one with daily baths of plain water only and the other with daily baths of a Castile soap and water, both without the use of any lotions or oil. It is of interest to note that on both services the supervising nurses complained so vehemently about the excessive number of rashes and dry skins met with under these two methods that it was felt advisable to return to the use of a lotion after one month's trial with each of these methods.

Fortunately there was only one important change in the personnel observing these patients during this entire study, so that it was felt that the variable of individual differences of opinion was eliminated as nearly as possible. The repeated interchange of the method used in the two groups at the above-stated intervals seemed to overcome the revealed tendency of one observer to detect a higher incidence of rashes than the other, as well as to compensate for seasonal variations.

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12. Loction A was supplied by The Wm. S. Merrell Company, of Cincinnati, and contains Ceepryn Chloride (cetyl pyridinium chloride) in a 1 : 500 dilution in a stabilized emulsion of lanolin, pectin, and minera oil. It is marketed under the trade name of Serene.

13. Lotion B was supplied by The Mennen Co., of Newark, N. J., and contains Purateen (methylbenzethonium chloride) in an emulsion of cholesterol and related sterols and a small amount of lanolin. It is marketed under the trade name of Mennen's Baby Magic Skin Care.

RESULTS

Incidence of various types of rashes (numbers and percentages) are shown in the accompanying tabulation.

	No. of Cases	Dry Skin		Miliaria		Inflamed Buttocks		Pustular Rashes		Total Rashes		% After 1 Wk.
		No.	%	No.	%	No.	%	No.	%	No.	%	
Lotion A group	1,481	143	9.6	104	7.0	96	6.4	28	2.0	371	25.0	4.4
Lotion B Group	1,668	74	4.4	73	4.4	159	9.5	23	1.4	331	19.8	8.2
Plain water	169	60	35.5	15	8.9	19	11.2	3	1.8	97	57.0	87.5
Soap and water	173	26	15.0	27	15.6	14	8.0	1	0.6	68	39.3	72.0
Grand totals	3,491	303	8.7	219	6.3	288	8.2	55	1.5	867	24.8	16.0

Follow-Up.—Of approximately 200 patients discharged from the hospital with rashes who were regularly followed in the outpatient department all of whom were given daily applications of Lotion B, 8% were reported as completely cleared in one week and 80% in one month, with 12% persisting beyond one month.

It was also noted that the majority of persistent rashes reported in the last two groups under A (plain water and soap and water) fell into the categories of either miliaria or dry skins and responded rapidly to the use of Lotion B.

COMMENT

Toxicity.—In no instance was there any evidence to suggest that any of the methods employed in this study resulted in any sensitivity reactions. This had been previously reported in the earlier study with Lotion A and was also reported in a personal communication [14] of studies done with Lotion B at the St. Michael's Hospital in Newark, N. J. Here 40 infants were patch tested without reaction, and a large number of newborn babies were treated with the lotion with no untoward reactions.

The relatively high incidence of rashes in general (25% of all infants showing some form of rash at some time during this first week of life) as compared with other reported studies is, we believe, a truer index of the actual incidence and is the result of careful daily observation for any rash that could fall into one of these four categories. The fact that well over 90% of these noted in the two main study groups had cleared within one week gives a truer picture of the usual findings when a newborn baby is discharged from the hospital. It also should be noted that of the 55 patients reported as having pustular rashes only 5, or 0.14%, of all the patients, had lesions of sufficient size and number to justify a possible diagnosis of impetigo, and all of these cleared promptly within one week—with two patients treated with an antibiotic ointment.

Neither the differences found in the number of pustular rashes nor the percentage of inflamed buttocks in the four series appear statistically particularly significant, except that the Lotion A group showed the lowest incidence of inflamed buttocks. In the two categories miliaria and dry skin the differences were most marked. Here the two water groups show from two to three times as many cases of miliaria as the lotion-treated groups, while dry skins were noted more than twice as frequently in the group treated with Lotion A as in that treated with Lotion B and three and seven times as frequently in the soap-and-water and plain-water

14. Maggio, George A.: Personal communication to the author.

groups, respectively. Remembering that Lotion B is a cholesterol-ester base lotion as compared with the oil-and-water emulsion of Lotion A and the water base of the other two groups this marked difference seems readily explained.

The bacteriostatic effectiveness of the quaternary antiseptic present in Lotion B in the percentage used therein was tested through the courtesy of Dr. S. M. Peck [15] with results comparable to similar studies of like antiseptics. Of special interest was the result obtained when Bacterium ammoniagenes was the test organism. Inasmuch as the daily application of such preparations to the infant skin appears to have a beneficial effect during the newborn period in decreasing the number of rashes present and in promptly clearing up the vast majority of those that did develop, their use throughout infancy would seem to have all the advantages reported for the chemically similar diaper rinses, powders, and ointments without the disadvantage of requiring an additional procedure in the infant's daily care.

SUMMARY

The literature of the past decade in regard to methods used for the prevention and treatment of rashes in the newborn baby is reviewed and the obvious lack of unanimity noted. Such comparative studies of various methods as have been reported are summarized. A report is given of the results obtained with the routine daily use in a modified "no bath technique" of two lotions containing quaternary antiseptics compared with a series in which plain water was used and one in which soap and water were employed. The apparent benefits of the lotions used and the particular nondrying effect of the one with a cholesterol-type base was demonstrated and its routine use in the prevention and treatment of dermatoses in infants suggested.

230 N. Broad St.

15. Peck, S. M.: Personal communication to the author.

Nursery supervisors Evelyn Andressen, R.N., Dorothy Rush, R.N., and Josephine Lucca, R.N., helped with this study.

Case Reports

BILE PERITONITIS IN INFANCY

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AND
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BILIARY peritonitis is an uncommon disease of childhood, usually produced by rupture of the biliary system from trauma, infection, or obstruction. Extremely rarely, it has been caused by the spontaneous rupture of a congenital defect in the biliary system.

Such a case was recently encountered at the Boston City Hospital.

REPORT OF A CASE

A 3-week-old baby girl was admitted to the Boston City Hospital on June 17, 1949, with a brief history of pain and marked restlessness. The infant delivery had been normal in every respect, and only three days prior to admission she had been examined in a well-baby clinic and found to be in good health—weighing 10 lb. 6 oz. (4,700 gm.).

The day prior to entry, the patient began crying, simultaneously drawing her legs up over the abdomen and becoming restless. During this day, she continued to take her feedings without vomiting and had a normal pale-yellow bowel movement. Following a fairly comfortable night, the patient began crying almost continuously and refused all her feedings. There was no bowel movement except for the passage of a small amount of "whitish mucus" some six hours before entry to the hospital. At no time did the patient vomit or pass blood by rectum.

Physical examination revealed a well-nourished and well-developed acutely ill infant who was crying almost constantly and drawing her legs over her abdomen. Generalized abdominal spasm and moderate abdominal distention were present. Palpation of the abdomen revealed generalized tenderness. Findings on rectal examination were normal in all respects. The rectal temperature was 102 F.; pulse rate, 130; respiration, 60, and weight 10 lb. (4,540 gm.).

The white blood cell count was 22,000. X-ray of the abdomen revealed a large gas bubble in the stomach and gas in the colon with no evidence of unusually dilated loops of the small or the large bowel or demonstrable fluid levels.

The preoperative diagnosis of appendicitis was made, and following the insertion of a Levin tube and the administration of a dextrose and isotonic sodium chloride solution clysis the operation was performed.

Under adequate ether anesthesia, a right rectus muscle-splitting incision was made. When the peritoneal cavity was entered, 100 to 150 cc. of bile-stained fluid was encountered and aspirated. Subsequent exploration of the general peritoneal cavity disclosed that the viscera along the right side of the abdomen were stained yellow. The appendix was normal, and there was marked dilatation of the stomach and the proximal small bowel. Because of the presence of bile in the peritoneal cavity, the abdominal incision was lengthened, and attention was directed to the right upper quadrant. The gall bladder was deeply embedded in the right lobe of the liver and was completely solid. Although inflammation was present along the serosa of the gall bladder, no site of perforation could be found. Several small pea-sized yellow-green cystic masses were discovered at the junction of the cystic with the common duct in the hepatoduodenal

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ligament. One of these was ruptured and appeared to have been the site of the bile extravasation. Figure 1 demonstrates these operative findings. No other congenital deformities of the biliary tract were found. A rubber drain was placed in Morison's pouch and brought out through a stab wound of the abdomen which was closed in the usual manner.

The patient had a smooth uncomplicated convalescence. The postoperative icteric indices were never higher than 5. She has been seen off and on for the past two years and has had no difficulty referable to her biliary system. Several attempts were made to obtain a cholecystogram but these failed owing to the patient's lack of cooperation.

COMMENT

Two published reports of biliary peritonitis in infancy have been found in the available literature. Caulfield reported two cases produced by obstruction.[1] The first case was that of a 6-week-old boy in whom obstructive jaundice developed fol-

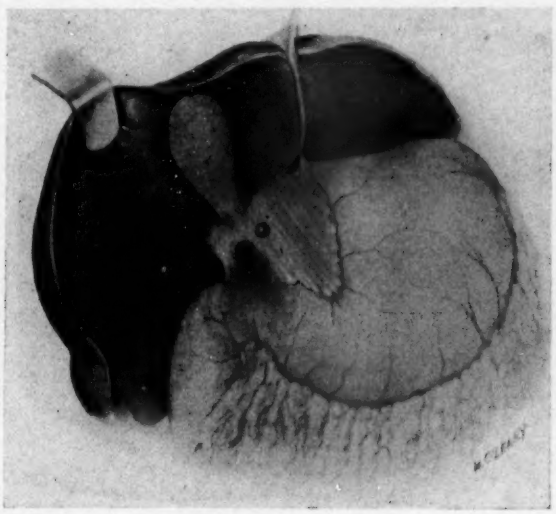

Fig. 1.—Artist's conception of operative findings in reported case. The salmon-pink gall bladder was deeply imbedded in the liver and was completely solid. In the gastrohepatic ligament two yellow-green pea-sized cysts could be found at the region of the junction of the cystic and common ducts. The inferior cyst had ruptured, spilling bile over the entire peritoneal cavity and staining most of the structures on the right side of the abdomen.

lowed by abdominal distention and shifting abdominal dullness. Laparotomy revealed massive biliary extravasation, which was successfully treated by drainage of the abdomen. The second case was that of an 11-week-old child in whom obstructive jaundice developed which subsided as abdominal distention developed. This child died, and autopsy disclosed a massive biliary peritonitis caused by the rupture of the biliary system from an obstructing congenital stenosis of the common duct. Hindmarsh reported a 22-month-old girl in whom abdominal distention and generalized abdominal tenderness with associated shock developed.[2] Laparotomy revealed 500 cc. of bile-stained fluid in the region of the gall bladder with no abnor-

1. Caulfield, E.: Bile Peritonitis in Infancy, Am. J. Dis. Child. **52**:1348, 1936.

2. Hindmarsh, F. D.: Bile Peritonitis in Infancy, Brit. M. J. **2**:131, 1947.

mality visible in the biliary system. The patient responded to abdominal drainage. Findings on a subsequent cholecystogram were normal. This is the only case found in which the bile extravasation in infancy was not caused by trauma, infection, or obstruction.

The occurrence of the solid gall bladder in association with multiple cysts in the region of the common duct suggests strongly that this malformation of the biliary system in the reported case is of developmental origin. It is to be remembered that in the fourth week of embryonic life a diverticulum arises from the ventral wall of the primitive foregut and grows into the transverse septum of the embryo. The

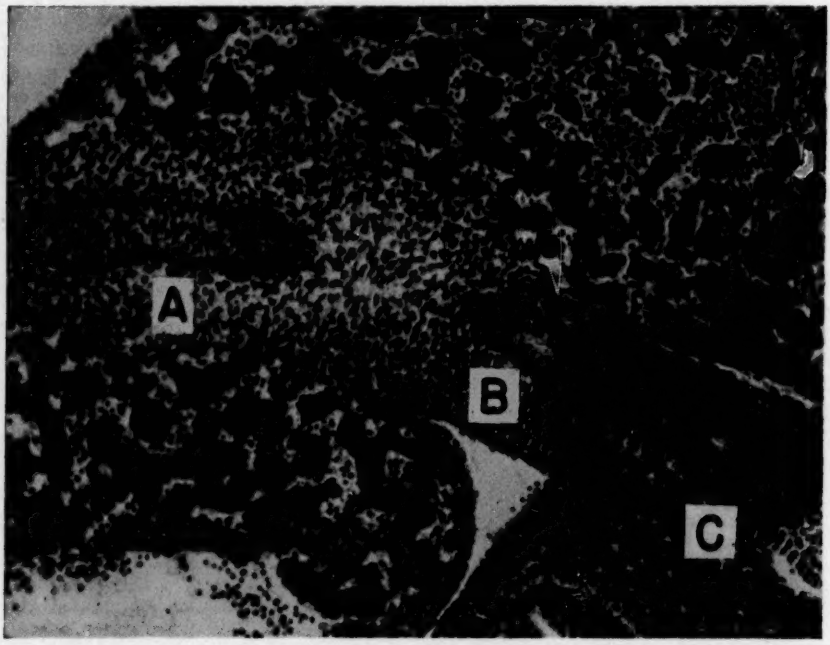

Fig. 2.—Cross section of a 12-mm. human embryo (obtained for study from the embryology collection of the Boston University School of Medicine). *A* indicates the completely solid gall bladder; *B*, the hollow common duct, and *C*, the hollow duodenum.

cranial portion of this diverticulum will later differentiate into the liver and the hepatic duct, and the caudal end will become the gall bladder, the cystic duct, and the common duct. At this stage the anlagen are hollow. However, as the epithelium proliferates, the gall bladder and bile ducts appear as solid cords of tissue. The further development of this system has been well described by Lewis [3]:

> At 7.5 mm., there is a lumen in the common bile duct, but the gall bladder is impervious. Near the hepatic duct, the lumen is sub-divided, appearing in cross sections as two or three minute pores. At 16 mm., there are irregular sub-divisions near the hepatic duct and the distal part

3. Lewis, F. T., in Bardeen, C. R., and others: Manual of Human Embryology, edited by F. Keibel and F. P. Mall, Philadelphia, J. B. Lippincott Company, 1910, Vol. 2, p. 410.

of the gall bladder is solid, but in both the cystic duct and common duct the lumen is single and well defined. . . . As the gall bladder expands, it may present intra-epithelial cysts. . . . At 18 mm., the greater part of the gall bladder has a clear-cut round lumen.

Figure 2 is the cross section of a 12-mm. human embryo obtained for study from the embryology collection of the Boston University School of Medicine. It demonstrates readily the developmental stage at which the gall bladder is completely solid and the cystic duct hollow. This may be the stage at which the congenital defect in the reported case developed. The process of vacuolization of the gall bladder may have miscarried so that the gall bladder never became hollow, and cysts appeared in the proximal biliary tract.

The future of this young child is, of course, conjectural. A full-blown choledochal cyst with its attendant triad of symptoms may develop, i. e., abdominal mass, jaundice, and temperature. On the other hand, the proliferation of the gall bladder may continue, and a neoplastic process may develop. The clinical course of this patient will be carefully followed in the years to come.

SUMMARY

The case of a 3-week-old child in whom biliary peritonitis was caused by a rupture of a congenital cyst in the region of the cystic duct is presented. This appears to be the second similar case found in the available literature.

Dr. William C. Barrett Jr., Associate Professor of Anatomy, Boston University School of Medicine, assisted the authors in reviewing the embryology of the biliary tract.

HEMOPHILIC CONDITION IN A GIRL

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THE QUESTION of whether hemophilia can occur in the female aroused the early interest of students of the disease, and it continues to attract attention, because if an answer can be found, an advance will have been achieved in bringing about a better understanding of a baffling disorder.

Otto[1] in his classical article stated, "When the cases shall become more numerous, it may perhaps be found that the female sex is not entirely exempt, but, as far as my knowledge extends, there has not been an instance of their being attacked." In 1770 a case of hemophilia appeared in Tenna, a little village isolated in the Swiss Alps. By 1854 this community with a population of 105 had 16 bleeders: 5 females and 11 males. The bleeding tendency of the women, however, consisted only of profuse menstruation.[2] It is very probable that some carriers were married to bleeders, but it is not possible to state whether these five females were the offspring of such a marriage or even whether they actually were true bleeders.

The genetic possibility that a daughter born of a hemophilic father and a carrier mother might inherit the defect in the active state has long been recognized on the basis of hereditary laws, but proof for the hypothesis has not been forthcoming. Bulloch and Fildes[3] in their extensive survey of about 600 hemophilic families failed to find any women with hemophilia. Birch,[4] who probably studied the largest number of hemophiliacs in this country, likewise failed to find a single case in all the families that came to her attention.

Although a few bleeders with a prolonged clotting time and with the type of bleeding typical of hemophilia were observed and reported,[5] they failed to meet

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1. Otto, J. C.: An Account of an Hemorrhagic Disposition Existing in Certain Families, Med. Reposit. **6**:1, 1803.

2. Grandidier, L.: Die Hämophilie oder die Bluterkrankheit Liepzig, O. Wigand, 1855.

3. Bulloch, W., and Fildes, P.: Hæmophilia, Treasury of Human Inheritance, edited by Julia Bell, Galton Laboratory University of London, London, Cambridge University Press, 1911, Parts V and VI, Sec. XIVa.

4. Birch, C. L.: Hemophilia: Clinical and Genetic Aspects, Illinois Medical and Dental Monograph No. 4, University of Illinois, 1937.

5. Joules, H., and Macfarlane, R. G.: Pseudo-hæmophilia in a Woman, Lancet **1**:715 (March) 1938. Madison, F. W., and Quick, A. J.: Hemophilia-like Disease in the Female: With a Note on the Clotting Time of the Recalcified Plasma, Am. J. M. Sc. **209**:443 (April) 1945.

one of the essential characteristics of true hemophilia, namely being congenital and hereditary in origin. In 1951 Israels and his associates [6] studied a case which appears to fit closely the criteria on which the diagnosis of hemophilia is made at the present time. This patient has a hemophilic father and a carrier mother. The possibility of hemophilia in women is further strengthened by the work of Brinkhous and his associates,[7] who demonstrated that in dogs with a bleeding disease similar in its hereditary and physiological characteristics to human hemophilia, the mating of male bleeders and female carriers resulted in female bleeders.

Recently the opportunity presented itself to study a girl in whom easy bruising was noted when she was 5 months old and in whom both clinical history and laboratory findings are almost indistinguishable from true hemophilia. Since both her father and mother are normal, one is confronted with the perplexing problem to decide whether this case should be regarded as hemophilia. If the decision is made that it is not hemophilia, then one must assume that it represents a clinical entity congenital in nature, which closely simulates true hemophilia. Should that be the case, then there is a possibility that such a condition may also occur in the male and this would present the bewildering problem of distinguishing between hemophilia and this new entity. Because of the important implications, the studies made on this patient are given in detail.

REPORT OF A CASE

D. L., a girl, was born June 16, 1949. Her development, growth, and nutrition have been entirely normal. Since the age of about 5 months, easy bruising has been noted. No illness, medication, or blood transfusion preceded this bruising tendency. At the age of 15 months, she complained of pain under her knee. In two days this was followed by marked swelling. Apparently the hematoma was too deep to cause discoloration of the skin, but a month later she had a large bruise with swelling on her buttock. When she was first seen by us, Nov. 27, 1951, she had a hematoma on the left side of her forehead which was about 2.5 cm. in diameter. This had been caused by a rather trivial bump.

Following her first visit, she had no serious bleeding until May, 1952, when she had painful swelling in the calf of the left leg. She was unable to walk for several days. A fall from her tricycle resulted in a large bruise on her buttock. She also had pain in her ankle severe enough to cause limping.

She was seen again Sept. 3, 1952. At that time she had a large ecchymotic area on her left upper arm and a smaller one on her right arm. A hematoma about 0.5 cm. in diameter was found in her scalp above her right ear.

Other than her bleeding she has had no sickness. She has had no hematuria, melena, or epistaxis. Minor cuts do not bleed abnormally.

Physical Examination.—Other than the ecchymotic areas in her skin and hematomas, no abnormality was observed. She is well nourished and her development is normal.

Family History.—She has a brother born April 27, 1951, who is normal. He did not bleed after circumcision and does not bruise. The father, who had just returned from military service, is well and free of any hemorrhagic tendency. Extraction of teeth, tonsillectomy, and various minor operations have not caused abnormal bleeding.

The mother is well. She has a slight tendency to bruise, but not more than is observed in many normal women. Her menses are normal and she had no abnormal hemorrhage following

6. Israels, M. C. G.; Lempert, H., and Gilbertson, E.: Hæmophilia in the Female, Lancet **1**:1375 (June) 1951.

7. Brinkhous, K. M.; Graham, J. B.; Penick, G. D., and Langdell, R. D.: Studies on Canine Hemophilia, in Transactions Fourth Conference on Blood Clotting and Allied Problems, edited by J. E. Flynn, New York, Josiah Macy, Jr. Foundation, 1951, p. 51.

the birth of her two children. In neither the father's nor the mother's family is there any record of any abnormal bleeding.

Laboratory Studies.—Although the tests employed in this study have been described in detail,[8] a short summary of the techniques and a few comments on interpretation as applied to the present case are presented in order to make the study of the patient's condition more understandable.

Collection of Blood: Silicone-coated syringes and needles were used and the blood immediately transferred to silicone-coated (Dri Film 9987, General Electric Company) test tubes immersed in an ice bath. Pipettes employed to measure and transfer the blood likewise were treated with silicone.

Clotting Time: A standardized technique of the Lee-White method was employed. Exactly 1 cc. of blood was placed in a scrupulously clean dry test tube (13 mm. by 100 mm.). The test tube was placed in a water bath at 37 C. and tilted every 30 seconds until a solid clot formed. The usual range for normal subjects is 5 to 8 minutes, but occasionally a value as high as 12 minutes is obtained. The most serious error is caused by the admixture of a minute quantity of tissue juice in making the venipuncture. In babies and young children a satisfactory collection is particularly difficult.

Prothrombin Time: The one-stage method was used. Only thromboplastin preparations (acetone-dehydrated rabbit brain) were used which gave 12 seconds in normal controls.

Total Prothrombin Time: When plasma is depleted of platelets by high centrifugation and then allowed to clot in glass, the resulting serum has a prothrombin time of eight to nine seconds. In carrying out the determination of the prothrombin time of serum, the fibrinogen is resupplied by fresh rabbit plasma from which the prothrombin has been removed by adsorption with tricalcium phosphate. The actual test consists of adding 0.1 cc. of serum to a mixture of 0.1 cc. deprothrombinized rabbit plasma, 0.1 cc. thromboplastin reagent, and 0.1 cc. 0.02 M calcium chloride and accurately timing the speed of clotting.

It may be postulated that the augmented prothrombin activity in serum is due to an actual increase of prothrombin.[9] Experimental evidence has been presented to show that prothrombin in human blood is present partly in an inactive form to which the term prothrombinogen has been assigned and partly in the free state. It is only the latter fraction of prothrombin which is measured by the one-stage procedure. In contact with glass the prothrombinogen is rapidly activated during clotting at 37 C., therefore all the prothrombin is then present in the free state. By depleting the plasma of platelets, no thromboplastin can form, and therefore no prothrombin is consumed. The prothrombin time of the serum under these conditions becomes a direct measure of the total prothrombin. An alternative explanation has been offered, namely, that an accelerator agent different from the known clotting factors is evolved to account for the increased prothrombin activity of serum.[10] Irrespective of which hypothesis is the more correct, the fact remains that the total prothrombin time of adult blood is very constant, and becomes prolonged in vitamin K deficiency and after the administration of bishydroxycoumarin (Dicumarol).

The Prothrombin Consumption Time: This test is based on the loss of prothrombin activity that occurs when blood is clotted under standardized conditions. The greater the amount of available thromboplastin, the less prothrombin remains in the serum. It is postulated that the thromboplastin formed in the blood is the resultant of a platelet factor and a plasma constituent (thromboplastinogen). As already stated, the removal of platelets from plasma brings about an apparent increase in prothrombin when clotting in glass occurs, because the prothrombinogen is

8. Quick, A. J.: The Physiology and Pathology of Hemostasis, Philadelphia, Lea and Febiger, 1951.

9. Quick, A. J., and Stefanini, M.: The State of Component A (Prothrombin) in Human Blood: Evidence that It is Partly Free and Partly in an Inactive or Precursor Form, J. Lab. & Clin. Med. **34**:1203 (Sept.) 1949. Quick, A. J., and Hussey, C. V.: Influence of Concentration of Thromboplastin on Prothrombin Time of Human and Dog Plasma, Proc. Soc. Exper. Biol. & Med. **76**:732 (April) 1951. Quick, A. J., and Hussey, C. V.: On the Comparative Prothrombic Activity of Human and Dog Blood, J. Clin. Investigation **30**:903 (Sept.) 1951.

10. Alexander, B., and Landwehr, G.: Evolution of a Prothrombin Conversion Accelerator in Stored Human Plasma and Prothrombin Fractions, Am. J. Physiol. **159**:322 (Nov.) 1949.

converted to the active state, and little is consumed. In hemophilia, the platelet factor is normal, but the thromboplastinogen is diminished; consequently, when hemophilic blood clots, much prothrombin remains unconsumed. The prothrombin time of the resulting plasma therefore will be short. When the deficiency of thromboplastinogen is very marked, the prothrombin consumption time is eight to nine seconds. In most hemophiliacs the range is 8 to 12 seconds.

The prothrombin consumption test is not specific for hemophilia. It is low whenever the available thromboplastin is reduced. This may be caused by a deficiency of platelets, a low thromboplastinogen level, and various other factors which will be discussed later. Failure of prothrombinogen to convert to prothrombin, or a deficiency of prothrombin may cause a false normal prothrombin consumption time.

Thromboplastinogen Activity Time[11]: The prothrombin consumption test is not specific because either a deficiency of the platelet factor or a lack of thromboplastinogen will give a low result. By adding a potent extract of platelets to blood or plasma before clotting, defective consumption of prothrombin becomes directly attributable to a deficiency of thromboplastinogen. It has been shown that when an extract of platelets is added to hemophilic blood the consumption of prothrombin remains low. This can be considered to be the most specific laboratory test for diagnosing hemophilia. It is employed in this study for that purpose. Unfortunately, however, the preparation of a potent platelet extract is difficult and time-consuming and, unless carefully controlled, may yield unreliable results.

A surprisingly easily prepared substitute for platelet extract was discovered. By heating a rabbit brain extract to 60 C. its thromboplastic potency is lost, but it retains the property of reacting with thromboplastinogen to form thromboplastin. When heated rabbit-brain extract is added to hemophilic blood, the prothrombin consumption remains low, but when added to either normal or thrombocytopenic blood good consumption of prothrombin occurs. The technique for doing the test is as follows:

Rabbit brain extract as prepared for the prothrombin time test is heated at 60 C. for 20 minutes. To a glass test tube (13 mm. by 100 mm.) containing four small glass beads 0.05 cc. of the heated thromboplastin reagent is added. Two cubic centimeters of blood is transferred to the test tube. After closing the tube with a paraffin-coated tissue (Parafilm) it is inverted several times to assure mixing and placed in a water bath at 37 C. for 15 minutes. The clot is loosened and the tube is centrifuged. The prothrombin time of the serum is determined 15 and 60 minutes after centrifugation.

The laboratory findings on Nov. 27, 1951, were as follows:

Clotting time (Lee-White)	8 min.
Bleeding time	3 min.
Prothrombin time	15-16 sec.
Total prothrombin time	9½ sec.
Platelet count	420,000 cu. mm.
Clot retraction	Normal

Prothrombin consumption time (determined 15, 30, and 60 min. after centrifugation):

	Sec.	Sec.	Sec.
Tube I	14	18	16
Tube II	..	8	11

Thromboplastinogen activity time: 9 sec.

Labile factor: Normal (Addition of deprothrombinized rabbit plasma did not correct the prothrombin defect.)

Because of the abnormal prothrombin time, the girl was given four capsules of a natural vitamin K_1 concentrate (Klotogen, Abbott) and 4 to 5 mg. tablets of a synthetic water-soluble vitamin K compound (Synkayvite), which she took during 24 hours.

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11. Quick, A. J.; Stapp, W. F., and Hussey, C. V.: The Effect of Heating on the Thromboplastic Activity of Rabbit Brain Extract: A New Test for the Diagnosis of Hemophilia, J. Lab. & Clin. Med. **39**:142 (Jan.) 1952. Quick, A. J., and Hussey, C. V.: Hemophilia: Clinical and Laboratory Observations Relative to Diagnosis and Inheritance, Am. J. M. Sc. **223**:401 (April) 1952. Quick, A. J., and Epstein, E.: Thromboplastic Activity in Human Blood, J. Appl. Physiol. **4**:840 (May) 1952.

The laboratory findings on Nov. 28 were as follows:

Clotting time	10½ min.
Prothrombin time	14½ sec.
Total prothrombin time	9½ sec.

Prothrombin consumption time:

	Sec.	Sec.	Sec.
Tube I	11	12	12
Tube II	..	10½	11

Thromboplastinogen activity time 10½ sec.

The laboratory findings on the girl's grandmother, who served as a control, were as follows:

Clotting time	7 min.
Prothrombin time	12 sec.
Total prothrombin time	8 sec.

Prothrombin consumption time:

	Sec.	Sec.	Sec.
Tube I	8	19	19
Tube II	..	12	18½

Thromboplastinogen activity time 15 sec.

To determine whether the patient's blood would correct hemophilic blood, the prothrombin consumption times on the following mixtures were ascertained:

	Volume of Blood in Cc.					
Patient's blood	1	1	..	2	..	..
Hemophilic blood	1	..	1	..	2	..
Normal blood	..	1	1	..	..	2
Prothrombin consumption time	9½	17	17	12	8	25

The patient was again seen Sept. 31, 1952. At this time her family was also studied. The results are summarized as follows:

	Patient	Brother	Father	Mother
Clotting time in min.	8½	6	9	8
Prothrombin time in sec.	14½	12	13½	13
Total prothrombin time in sec.	9½	8½	8½	8½
Prothrombin consumption in sec.	12½	35	27	30
Thromboplastinogen activity time in sec.	11½	22	14	19

The effect of the patient's blood on that of a known hemophiliac was again determined. The results are summarized as follows:

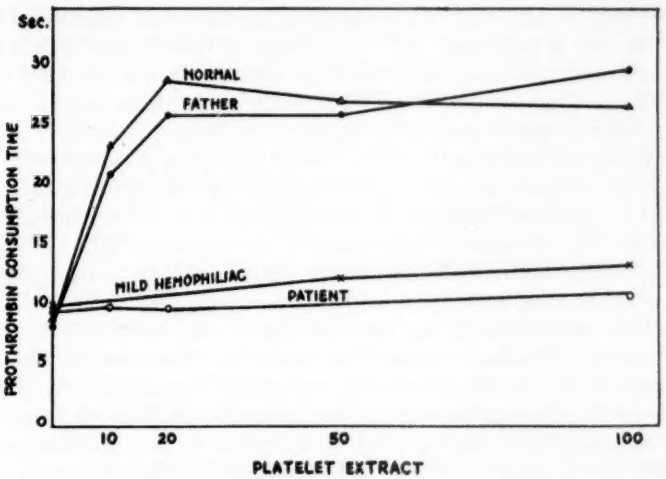
	Volume of Blood in Cc.					
Patient's blood	1	1	..	2	..	..
Hemophilic blood	1	..	1	..	2	..
Normal blood	..	1	1	..	..	2
Thromboplastinogen activity time in sec.	13	33	40	11½	9	40

To verify further that the defective consumption of the patient's blood was caused by a deficiency of the plasma factor, the effect of a potent extract of platelets on the utilization of prothrombin was determined (Chart).

CRITERIA FOR THE DIAGNOSIS OF HEMOPHILIA

The diagnosis of hemophilia on the familiar triad of a bleeding tendency, a prolonged coagulation time, and a characteristic hereditary pattern is most helpful, but it has serious limitations. This is brought out by the data which summarize the findings of 25 hemophiliacs recently studied (Table). It will be noted that in less than one-half of the cases could heredity of the disease be established. A similar percentage was noted in previous series.[12] In all cases the bleeding tendency

12. Quick, A. J.: Management of Hemophilia in General Practice, J. A. M. A. **145**:4 (Jan.) 1951.



The influence of added platelet extract on the prothrombin consumption time. Like a true hemophiliac, the patient's clotting defect is not corrected by an excess amount of platelet extract. The father's response is normal. The test and the preparation of the required material have been described.[11]

Summary of Findings in Twenty-Five Hemophiliacs

Subject	Age, Yr.	Clotting Time, Min.	Prothrombin Consumption Time, Sec.	Thromboplastinogen Activity Time, Sec.	Prothrombin Time, Sec.	Total Prothrombin Time, Sec.	Heredity	Clinical Course
G. F.	5	11	13½	9	12	8	+	Mod. mild
K. Z.	17	45	8½	9	12½	8½	+	Mod. severe
R. J.	4	30	9	9	12½	8	—	Mod. severe
D. W.	1	9 (?)*	8	8	12	8	+	Mod. severe
H. L.	39	11½	18	9	12	9	+	Mod. mild
D. L.	3	56	9	9	13½	9	F †	Severe
R. L.	1	9½ (?)*	9½	9½	12	8	F	Severe
C. P.	55	11	21	10	12	9	F	Mild
M. R.	4	55	8	8	13	8½	—	Severe
J. L.	7	60	9	9	12½	8	—	Severe
P. L.	8	14	9	10	12	9	—	Mod. severe
J. D.	21	15	9½	9	12	8	+	Severe
V. V.	45	13	24	13	12	8	+	Mild
R. S.	35	22	9	8½	11½	8	+	Mild
M. H.	5	12	22	11	12	8	+	Mild
D. S.	17	30	10	10	13	9	+	Severe
M. M.	10	10	16	10	12	9	+	Mod. severe
E. J.	2	55	9	10	12	9	—	Severe
C. C.	7	115	10	10	12	9½	—	Severe
J. F.	10	135	10	9½	12½	9	F	Severe
P. F.	12	110	10	9½	13	9½	F	Severe
W. F.	4	65	8½	8½	12	8	+	Severe
C. K.	62	105	12	10½	12	8	+	Mod. mild
A. A.	½	40	9	11	12	..	—	Severe
R. Z.	20	135	11	12	12	9	—	Mod. severe

* Unsatisfactory collection of blood.
† F indicates familial, i. e., two or more brothers with a hemophilic condition, but no history of hemophilia in the family.

manifested itself in infancy or early childhood. In the great majority of patients the clotting time is prolonged, but in a number of hemophiliacs with a positive family history and well established bleeding tendency the clotting time is within the range found in normal individuals. The prothrombin consumption is invariably low in moderately severe cases of hemophilia, but in very mild cases it may be normal. While this somewhat limits its clinical usefulness, it nevertheless remains a valuable test for estimating the degree of thromboplastinogen deficiency.

The most consistent results have been obtained with the thromboplastinogen activity test. This is clearly demonstrated by the cases in Table 1. While the test is somewhat empirical and does not run parallel with the clotting time or the severity of the bleeding tendency, it has been consistently positive in about 50 cases of hemophilia studied during the past two years. On the basis of the present finding it seems justifiable to conclude that if the thromboplastinogen activity time is more than 13 seconds, the diagnosis of hemophilia is very doubtful. A value of 13 seconds or less does not, however, by itself establish the diagnosis of hemophilia. The thromboplastinogen activity time varies greatly in normal individuals and occasionally it may be as low as 14 to 15 seconds for no obvious reason.

IS THE PATIENT'S CONDITION HEMOPHILIA?

Clinically, the girl's condition is indistinguishable from hemophilia. The tendency to bruise was noted at the time she began to crawl, and she has had various types of bleeding typical of hemophilia. Since she had no other illnesses, it is most unlikely that it is an acquired condition. Her father and mother are normal, and there is no record of bleeding in the family. Since no hereditary history can be established in many cases of hemophilia, this does not rule out the diagnosis of hemophilia.

The laboratory findings further emphasize the similarity of this girl's disease to hemophilia. The clotting time, to be sure, is not prolonged, but the difficulty of getting blood from a small vein without a trace of tissue juice may well cause a shortening of several minutes. Then, too, a normal clotting time in mild hemophiliacs has been observed by both Merskey and by us.[13] The prothrombin consumption and the thromboplastinogen activity are both unmistakably low. Hemophilic blood is not corrected when her blood is added; but both her blood and that of a hemophiliac are corrected by the addition of an equal volume of fresh normal blood, thus showing that her blood does not contain a circulatory anticoagulant. It appears therefore that she lacks the same agent which is low in hemophilic blood, namely, the thromboplastinogen fraction.

The one abnormality in her blood that differs from true hemophilia is a mild reduction of her free and total prothrombin which is not corrected by vitamin K. While the hypoprothrombinemia is probably too slight to be an important influence on her bleeding, it nevertheless is consistently constant. Her labile factor is normal. Although a slightly prolonged prothrombin time is occasionally found in hemophilia, it is promptly corrected by vitamin K. Whether her hypoprothrombinemia is coincidental to the thromboplastinogen deficiency or is part of a specific congenital state can be determined only when other cases are found and studied. It is interesting to note that both the father and the mother had a slightly prolonged prothrombin time. There was no opportunity to ascertain whether this was only temporary or fixed.

13. Merskey, C.: Haemophilia Associated with Normal Coagulation Time, Brit. M. J. **1**:906 (April) 1951. Quick, A. J.: Pediatric Aspects of Hemophilia, Pediatrics **3**:312 (March) 1949.

The patient studied by Israels and his associates had laboratory findings similar to those observed in our patient. The important difference was that their patient had a hemophilic father and a carrier mother. Recently Merskey [14] reported two additional cases in which the laboratory data correspond to that of hemophilia. Since the condition was transmitted, however, directly from father to son in several generations, one must be cautious in the acceptance of these as cases of true hemophilia. Schulman and Smith [15] have reported a male patient with a bleeding tendency similar to hemophilia, but due to a lack of a factor which they believe is different from thromboplastinogen. Aggeler and his associates [16] have also reported an atypical case. These reports emphasize the increasing complexity of the problem of recognizing true hemophilia.

It is already known that a circulating anticoagulant may arise which not only prolongs the clotting time of normal blood, but even lowers the prothrombin consumption. This acquired hemophilic-like disease happens to be easily differentiated from hemophilia. The prolonged clotting time of hemophilic blood is corrected by the addition of normal blood, but this does not occur when the blood contains the anticoagulant. Perhaps other conditions with low thromboplastinogen activity, even when congenital, may not be true hemophilia, but because of inadequate tests it is not possible at present to distinguish them from hemophilia. If there is uncertainty as in the case of the female hemophiliacs, it might perhaps be best to use the term "hemophilic condition." When more specific diagnostic procedures are developed, the true status can be established.

In the interim, while more precise methods are awaited, the introduction into the hospital laboratories of the existing tests such as the total prothrombin time, the prothrombin consumption method, and the thromboplastinogen activity time will help considerably in putting the diagnosis and therapy of the various bleeding diseases, particularly hemophilia, on a sounder basis. Whether or not it is possible to differentiate hemophilia from a condition closely simulating this disease is not too important at present therapeutically, since the management and treatment would probably be the same for both. In the guidance of the patient in respect to the transmission of the defect, accurate diagnosis is of utmost importance. If there is uncertainty it is best to err on the conservative side and regard any atypical case as hemophilia.

SUMMARY

A case of a bleeding disease in a girl closely simulating hemophilia both clinically and in laboratory findings is presented. The diagnosis of hemophilia is discussed.

Dr. Robert Peers Buckley, Duluth, Minn., gave permission for the authors to study and describe this case.

14. Merskey, C.: Haemophilia Occurring in the Human Female, Proceedings Third International Society of Hematology, New York, Grune & Stratton, Inc., 1951, p. 441.

15. Schulman, I., and Smith, C. H.: Hemorrhagic Disease in an Infant Due to Deficiency of a Previously Undescribed Clotting Factor, Blood **7**:794 (Aug.) 1952.

16. Aggeler, P. M.; White, S. G.; Glendening, M. B.; Page, E. W.; Leake, T. B., and Bates, G.: Plasma Thromboplastin Component (PTC) Deficiency: A New Disease Resembling Hemophilia, Proc. Soc. Exper. Biol. & Med. **79**:692 (April) 1952.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

George F. Munns, M.D., President
Regular Meeting, Dec. 16, 1952

Marfan's Syndrome with Aortic Aneurysm. Dr. H. S. Traisman, and Dr. F. R. Johnson (by invitation).

This case is presented because it demonstrates all the major and minor manifestations of Marfan's syndrome. A complete autopsy was obtained and revealed the presence of aneurysmal dilatation of the aorta, never before reported in an infant.

The patient was a 9-month-old white boy, who was admitted because of "an enlarged heart, or lung tumor." There was a history of frequent respiratory infections. Examinations revealed arachnodactyly, fibrillation of the tongue, arthrogryposis, amyotonia congenita, and a harsh systolic apical murmur. There were rales and dulness over the right chest. Despite administration of oxygen and antibiotics, the patient died.

Autopsy revealed arachnodactyly, dislocation of the lens of the right eye, and congenital heart disease. This triad composed Marfan's syndrome. A severe bronchopneumonia was the immediate cause of death. The heart was about five times normal size. The left atrium and auricular appendage were extremely dilated and hypertrophied. Beginning in the sinus of Valsalva and extending peripherally for a distance of 2 cm. was a marked aneurysmal dilatation of the aorta, which subsided gradually as the arch of the aorta was reached. Microscopic examination revealed a medial necrosis of Erdheim.

Only six cases of Marfan's syndrome with aneurysmal dilatation of the aorta have been reported. The youngest patient was aged 13 years, and the remaining five were in the twenties. This is the first case to be reported in an infant.

DISCUSSION

Dr. E. William Immermann: I have seen two cases of arthrogryposis that have come to autopsy; one, Dr. Traisman's about four years ago at Children's Memorial Hospital. There was a definite diminution in the number of motor cells of the entire cortex, cerebellum, and spinal cord. It is felt on the basis of these two cases that the primary defect is neurogenic, rather than in the joints or muscles.

A number of years ago Dr. Stern defined the condition as "crooked joints," hence the name arthrogryposis. He felt that the primary defect was in the muscles per se. It is difficult to find muscle in the extremities on biopsy because of replacement by scar tissue. Thus as the child grows and the muscle does not, bone and joint deformity results. This has been found repeatedly. There are those who feel that the primary defect is in the joint itself, although at the time of surgery it has been observed that the joints are normal in appearance with deformity secondary. It is my feeling that these cases, which are progressive in nature, are on a neurogenic basis. Perhaps this is a significant factor in Marfan's syndrome.

Tumors of the Sternocleidomastoid Muscle. Dr. E. T. McEnery.

The tumor mass usually appears between the second and third week of life, and the majority of them are noted by the mother after the infant has gone home. Chandler describes the tumor as smooth, attached to the deeper structures, and freely movable beneath the skin. It is tense and semielastic. There is no induration of the soft tissues adjacent to the tumor and no ecchymosis of the overlying skin. On excision of the tumor there will be found fusiform masses involving part or all of the muscle belly, usually in its mid-third. The tumor is limited by the perimysium and may involve the entire muscle substance. It is firm and separates readily from adjacent structures. Cross sections reveal a white fibrocartilaginous glistening surface, which at times is slightly lobulated. Nothing has been found to suggest blood-clot formation

or residual blood pigment. On microscopic section, muscle fibers in all stages of degeneration may be found; fibrous tissue is abundant, replacing muscle fibers to varying degrees.

The work of Chandler has apparently disproved the theory that these masses were due to hemorrhage in the muscle. Several other theories have been advanced: Birth trauma—the condition is usually found in a difficult delivery, usually breech. On the other hand, it has been reported in Cesarean section. Ischemic hypothesis—pressure on muscle in utero, producing necrosis. Chandler, in reporting his large series, dissected out the blood supply in many newborn infants and found that the sternocleidomastoid muscle had an abundant blood supply. Intrauterine malposition—pressure of the shoulder against the belly of the muscle while the head is flexed on that side. None of these theories apply to all cases, although malposition seems to be the most plausible explanation.

In a series of 37 cases in which the patients were followed for at least one year, only one has been operated upon. In this case the mother did not adhere to the recommended treatment and brought the child back at the age of 3; the postoperative result was good.

Treatment should be started as soon as the diagnosis is made. The infant's head is placed on a small hard sandbag, thus bringing the muscle mass upward. A squeezing movement is used on the tumor, between the thumb and first finger, repeating this about 10 times. Then the thumb is pressed downward over the mass 10 times. The head is rotated from side to side 10 times. The whole routine is performed night and morning, usually by the father of the infant, as the mother has a tendency to use insufficient pressure. As a rule, the massage can be stopped at the end of three weeks with the disappearance of the mass. Head turning should be continued until the child is at least a year old.

In most cases good results are obtained by conservative treatment and, should operation be deemed necessary, it can be done before growth and development changes take place.

DISCUSSION

Dr. E. William Immermann: Treatment of the neglected patients is a surgical problem, when a regimen such as suggested by Dr. McEnery has not been carried out. Contrary to his experience, I have seen such a mass within the first week of life. It was very small. It is true that they tend to become larger. On the basis of Dr. Chandler's work, it is felt that not only does the position of the infant in utero play a part but that the trauma of delivery also plays a role. About 50% of the patients are born by breech deliveries, about 20% by difficult labors. With Cesarean section there is no trauma, but Chandler feels that a nonspecific inflammatory reaction is produced in a muscle which results in the pathology.

About four years ago I performed an autopsy on an 18-week-old baby who had been placed in a cast for severe torticollis secondary to such a mass, was given a feeding while on his back, aspirated the milk, and failed to respond to treatment.

The entire sternocleidomastoid muscles were dissected out bilaterally. These youngsters have a tendency to hold the side of the head toward the site of the tumor and rotate the chin to the opposite side. Many of them have deformities when they are born—deformity of the calvarium, distortion of the ear, a cervical or dorsal scoliosis. There is x-ray evidence of this intrauterine position, where the child is delivered having a mass in the sternocleidomastoid muscle. This youngster had a large mass in the neck which was demonstrated when the head was deviated to the opposite side.

On the abnormal side there is a marked tumor formation which is actually a fibroma with extensive fibrous tissue and few muscle fibers interspersed. It involves the entire sternocleidomastoid muscle, only one of the clavicular heads remaining normal.

Dr. McEnery pointed out that stretching and turning the head gradually improves the torticollis, with disappearance of the mass. There are a number of patients that are untreated and the mass disappears, but that is not the point. I think Dr. McEnery's treatment is ideal in keeping the muscle stretched, because as the tumor becomes smaller the fibrous issue is gradually replaced by hyaline connective tissue. On microscopic section, where the mass has disappeared, the contracted muscle may appear like a tendon. Thus the stretching and massage will keep the muscle stretched and prevent contraction as it is going through the stage of re-formation.

The cut section of the tumor, as Dr. McEnery pointed out, does not demonstrate any hemorrhage or hemosiderin or any evidence of hematoma which was formerly thought to be the cause

of these tumors. This section through the entire mass shows the hard fibrous consistency. On microscopic section the muscle fibers are in various stages of degeneration with interspersed fibrous tissue and scattered blood vessels and giant cells. This may all be replaced by connective tissue.

One child had a mass in the neck which was not treated and now has a contracted sternocleidomastoid muscle with its two well-defined heads demonstrating a tight hard hyalinized type of muscle. The sections show an extensive degree of hyalinization. Thus, the torticollis is on the basis of the residue of the mass which was not taken care of, which was allowed to persist without stretching of the neck to maintain the length of the sternocleidomastoid muscle.

I concur with Dr. McEnery that treatment consists of constant stretching, compression on the mass, placing the youngster in bed and holding him in such position that he has to deviate his head to the opposite side. Surgery should be reserved for those cases in which treatment has not been carried out, for children over 5 years of age, and those under 5 who have marked deformities, facial and ocular asymmetry, etc.

DR. PHILIP L. ARIES: When this subject was presented before this society several years ago, I was surprised to hear that so many patients were treated surgically. My impression was that these tumors disappeared spontaneously.

In 1951 I observed four children who had a sternocleidomastoid tumor. The first child I had seen twice, when 3 days old and 4 weeks old, and no tumor was seen or felt. When seen again at the age of 5 weeks there was a mass exactly of the type described by Dr. McEnery. Gentle passive manipulation of the head was carried out by a parent four times a day. A month later the swelling had entirely disappeared and there was no evidence of impaired function of the neck structures.

The second child was normal when examined at the age of 2 days and, when 3 weeks old, there was a tumor on the right side of the neck. At the age of 6 weeks the mass was smaller, and it had completely disappeared five weeks later. Reexamination a year later revealed no abnormality. In a third child nothing was noted at the age of 9 days, and two weeks later a tumor was found on the left side. At the age of 7 weeks there was marked improvement, the tumor receding and the neck being freely movable. This patient was not followed beyond that period. The fourth patient was normal when 2 days old. At the age of 5 weeks a tumor was noted on the right side, which disappeared when the child was 2 months old. Now, two years later, there is absolutely no residual pathology.

I recall another child whom I first saw at the age of 3 months, in 1937, and whom I still see occasionally. Her family was greatly disturbed because she had a tumor on the right side of the neck. I thought we were dealing with an organized hemorrhage which resulted from birth trauma and felt sure it would disappear. A month later, following passive manipulation of the neck muscles, the lesion was no longer present, and there has been no difficulty since.

About two years ago, Dr. Jeanette Hork permitted me to see a 5-month-old patient at Mount Sinai Hospital who had a tumor of almost bone-like consistency in the sternocleidomastoid muscle. The child had a torticollis, and there had been no evidence of regression of the tumor since first noted several months prior to hospitalizaton. I had to agree that this tumor required surgical management, which was carried out with subsequent cure.

DR. M. P. BOROVSKY: I had the same reaction to Dr. Chandler's presentation when I heard it, but still had the opinion that most of these tumors were hematomas that cleared spontaneously, in spite of an excellent discussion and pathologic presentation.

Within recent months I have had a case that will bear out some of the points Dr. Immermann mentioned. A baby was born at Presbyterian Hospital, delivered by one of the leading obstetricians. He admitted it was a difficult delivery. I saw the baby at the age of about 2 days, and it had a birth palsy involving the right arm. It was treated conservatively, the hand began to move and it looked as though things were coming along nicely. The baby went home about the sixth day and, about a week later, to my chagrin I felt a hard globular mass on the right clavicle which was obviously callus formation in a fracture of the clavicle. The hand was improving, but it seemed likely that the baby's distress was attributable to the fractured clavicle which had been overlooked. We were still more chagrined when the nurse described a mass in the baby's neck about three weeks later. A very firm mass in the right sternocleidomastoid muscle was found. In spite of treatment there was an increasing torticollis and,

at the age of 2 months, marked asymmetry of the face. The right side of the face was definitely flat and drawn, with prominence of the opposite side, and the head was held firmly to that side. On orthopedic consultation it was thought advisable to remove the mass which I thought was a hematoma; however, on microscopic examination it showed typical fibroma.

This child apparently had considerable trauma on the right side, and it seems that that might go with some of the factors mentioned by Dr. Immermann. I would not care to continue conservative treatment with a baby of that age in whom such marked changes had developed, although milder cases might respond without surgery. I wonder if Dr. McEnery would advocate conservatism in such a case.

DR. IWAN ROSENSTERN, Evanston, Ill.: Among 2,500 young infants admitted to the Cradle, in Evanston, during a 10-year period, there were 15 cases of muscular torticollis. All received conservative treatment, and in 14 cases the mass disappeared gradually; in only 1 case was surgery necessary.

DR. E. T. MCENERY: I thought there would be more discussion by orthopedic surgeons, but Dr. Immermann was very kind. Remember that these are newborn infants, not children 2 or 3 years of age with facial asymmetry. If they are seen between 2 and 3 months of age, I think they should be given a trial with conservative treatment.

This series of 37 cases is not large when compared with 225 or 300 cases that Chandler has seen, but included in his series are many children aged 5 and 6 and 10 years of age. Those that I think can be cured by conservative treatment are the ones seen early. I still have faith in physical therapy.

Dwarfism with Chronic Hypoglycemia and Convulsions: Observations with Corticotropin (ACTH), Cortisone, and Thyroid. DR. MATTHEW M. STEINER.

These observations were made on two dwarfed siblings, a boy aged 10 years and a girl aged 5 years, whose heights were 28 in. (50.8 cm.) and 23 in. (58.4 cm.), weights, 20 lb. (9.1 kg.) and 13 lb. (5.9 kg.), and bone ages 6 months and 3 months, respectively Body habitus was that of athyreotic cretins with mental development roughly consistent with bone age. The onset of hypoglycemic episodes ranged from shortly after birth to 5 months of age. There was no uptake of radioactive iodine over the thyroid region. Extreme sensitivity to orally administered thyroid was exhibited repeatedly; as little as 1/16 grain daily for four days produced marked weight loss and hypoglycemia.

Administration of 15 mg. of corticotropin (ACTH) four times daily resulted in an increase of fasting blood glucose from control values of 23 to 28 mg. per 100 cc. to values of 94 to 115 mg. per 100 cc. Later, with intermittent administration of corticotropin, a dose of 2.5 mg. once every 4 to 5 days was sufficient to maintain a fasting level of 52 to 72 mg. per 100 cc. and permitted tolerance to initial thyroid medication. Rapid increase in thyroid to 1 grain daily necessitated an increase of corticotropin to 15 mg. every 4 to 7 days in order to maintain blood glucose values above 45 mg. per 100 cc.

Interrupted doses of corticotropin, despite increasing daily amounts of thyroid, were sufficient to "buffer" the blood pressure against precipitous falls except for the cumulative effect (hypoglycemia with tremors) of large doses of thyroid.

Corticosterone (administered orally) with thyroid maintained satisfactory levels of blood glucose; a dose of 2.5 mg. daily gave fasting blood glucose levels of 40 to 60 mg. per 100 cc.

Corticotropin and cortisone did not affect markedly the serum cholesterol concentration. Eosinopenia developed with administration of corticotropin and cortisone. The increase under corticotropin-thyroid was discussed. Definite loss in weight occurred under prolonged corticotropin-thyroid therapy. There was no increase in body length.

Clinical improvement with administration of corticotropin or cortisone alone was characterized by increased appetite, gain in weight, better skin color and motor activity, loss of constipation, growth of scalp hair, and decreased size of tongue.

While the etiology of this syndrome remains obscure, it is postulated that the unusual dwarfism of these siblings is the result of an insufficiency of the anterior pituitary, perhaps secondary to a congenital defect of the hypothalamus, with fractional deficiencies of the hormones concerned with growth, thyroid, gonads, and adrenal cortex, and that the hypoglycemia is the result of hypofunction of one or more of these "target" organs.

DISCUSSION

DR. RACHMIEL LEVINE: I should like to stress the importance of studying such cases as Dr. Steiner presented, because they form the only approach we have to test whether some of the assertions derived from animal experiments are valid in the human being. The syndrome presented cannot be explained completely on the basis of pituitary insufficiency, because pituitary dwarfism is symmetrical, and the mental age is normal. The bone age is consistent with the picture of hypopituitarism, the mental retardation is not.

The thyroid insufficiency which follows hypopituitarism is usually not of the myxedematous or cretinous variety. The facies, especially that of the boy, was typical of a cretin. The adrenal defect was evident by the low blood sugar value, and especially by what happened to the blood sugar when the patient was under the stress of infection. In addition, the blood sugar fell when thyroid was given. In adrenal insufficiency, the administration of thyroid may precipitate a crisis.

It is puzzling that there was no great electrolyte disturbance. This would fit with a pituitary cause for adrenal insufficiency. The fall of eosinophiles after administration of corticotropin and epinephrine indicated what we would call a normal Thorne test. During the past year or so, evidence has accumulated that the drop in the eosinophiles after administration of epinephrine cannot be interpreted as being solely due to stimulation of corticotropin and the consequent secretion of steroids. In completely adrenalectomized animals, under certain conditions, epinephrine itself affects the eosinophile count. Therefore, I do not think we can interpret those tests as meaning that there was no adrenal defect. The adrenal defect was evident both from the behavior of the blood sugar, and from the way the blood sugar responded to the administration of cortisone.

One could suppose that the low blood sugar and the hypoglycemic reactions were associated with hypertrophy of the pancreas or an adenoma of the pancreas, but such conditions do not readily respond to small doses of cortisone and corticotropin. They will respond to very large amounts, but not to small ones. In general, if one gets a response to very small doses of any hormone, in a child or in an adult, it provides the best evidence that there was a deficiency of the hormone in that individual. The follicle-stimulating hormone output was very low, and that again points to a pituitary defect. I must say that I have never seen a pituitary dwarf that was retarded to this extent. We have seen pituitary dwarfs aged 8 or 9, or even 12 years of age, who looked like 5 or 6, but pituitary dwarfism of this variety, in which an individual 10 years old looks like a cretinous individual of 6 months, is unique. So one must assume other pathologic conditions. The brain, of course, is a very convenient place to assume lesions when one doesn't know where to place them elsewhere. This is especially true of the hypothalamus, since in this very small area there are many functions described by many authors. I should not like to make the assertion that this is hypothalamic; I may believe it, but I would not want to voice it. I think the best guess would be that these children suffer from a genetic dysfunction, especially because it expressed itself in two siblings in a similar fashion.

The evidence we have for the functional connection between the brain and the pituitary is very meager, since there are no nerve fibers, as such, in sufficient numbers that can be seen to go from the central nervous system to the anterior pituitary. Despite that lack, we know of many instances in which nerve stimuli are transmitted to anterior pituitary; adrenocorticotropic hormone release due to stress, thyrotropic hormone release following cold exposure, luteinizing hormone release on stimulation of the cervix, and so on. But at the present time we have no idea how the impulse arrives at the gland, except the suggestion that the nerve impulse goes to the hypothalamus, that the hypothalamus is a neuroendocrine system which secretes neurohumors, and that these find their way to the vascular system of the so-called portal circulation of the pituitary. This is an attractive theory except that it does not explain specificity of response.

If we stimulate the cervix in the rabbit, there is an output of luteinizing hormone and ovulation. If one produces a "stress" in the same rabbit, adrenocorticotropic hormone is secreted primarily. Chronic cold may evoke thyrotropic hormone secretion, etc. Such specificity requires either specific neurohumors or specific pathways.

Once again a clinical problem, an "experiment of nature," has raised more questions than our present level of knowledge can answer.

DR. RALPH H. KUNSTADTER: It occurred to me after listening to this paper and to Dr. Levine's discussion that possibly there was a significant disturbance of the adrenals in these cases, and this picture of hypothyroidism and hypopituitarism could be associated with a subclinical state of salt-and-water depletion, particularly in those instances in which the infants had respiratory infection and diarrhea. I was not impressed by the weight gain at the time when the adrenals were showing evidence of stimulation and apparent clinical improvement was taking place. I wonder what desoxycorticosterone and possibly some salt would do along with the other therapy.

The second question is, what can one expect by the use of cortisone over a long period of time, even in the small doses given, of diminution of adrenocorticotropic hormone output by the pituitary, and possibly also further depression of the thyroid? Also during protracted treatment there may be refractoriness to the drug, so that one may even defeat one's ultimate purpose.

DR. MATTHEW M. STEINER: I think we might ask any question about these children and I would not know what to answer, because I am as much in the dark as anyone. What I have done is to endeavor to keep these children alive and to see the response to various procedures.

I want to thank Dr. Levine for his illuminating remarks. Dr. Kunstadter's question is very provocative. The increase in weight with administration of corticotropin was obtained in the absence of any changes in salt or chloride. The blood chemistry was checked repeatedly. The changes with corticotropin were obtained in the absence of glycosuria and low ketonuria. So I think actually the increase in weight, which was rather significant, was due to increased intake in food. Whether that was primarily the action of corticotropin, of course, is difficult to say, but these patients did improve, eat more, and gain weight without the so-called edema effect seen with prolonged administration. This was really an acute experiment, for the corticotropin was administered for some 10 days.

The next question is interesting—whether using cortisone for such a length of time, even in small doses, will depress the hormone mechanism and produce refractoriness. That brings in more than one problem, one which Wilkins and many others have posed in the treatment of female pseudohermaphroditism when cortisone is being used to depress the output of 17-ketosteroids. Wilkins and others, and we in these patients, have given "corticotropin boosters" and obtained depression of eosinophiles. So we think that even with such small amounts over at least this length of time—it is now almost eight months—they still can react to administration of 10 mg. of corticotropin with a fall in eosinophiles. We do not think the cortisone is damaging the adrenal cortex.

Our attempt has been to keep these patients alive and keep them from becoming hypoglycemic and developing fatal convulsions. We have many more plans for these children; so-called growth hormone alone, growth hormone with thyroid, growth hormone, thyroid and cortisone, thyroid with male sex hormone, and various other combinations.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

SKELETAL CHANGES IN SEVERE PHOSPHORUS DEFICIENCY OF THE RAT. R. D. COLEMAN, H. BECKS, F. VAN NOUHUYS KOHL, and D. H. COPP, Arch. Path. **50**:209 (Aug.) 1950.

Severe rickets developed in growing rats restricted to diets very low in phosphorus (0.005 to 0.015%) despite the presence of presumably adequate amounts of vitamins A (25 U. S. P. units per gram) and D (8 U. S. P. units per gram). Roentgenograms showed a marked lack of mineral in the skeleton of deficient animals and a delay of skeletal maturation in the vertebrae. Signs of severe rickets were also found on histologic sections of bone. Metabolic balance studies revealed a negative phosphorus balance and loss of bone ash in the deficient rats. It appears that phosphorus may be recovered from bone to provide for the essential phosphorus needs of the soft tissue.

HAW CHAN, San Francisco.

EFFECT OF HEAT TREATMENT ON THE NUTRITIVE VALUE OF MILK PROTEINS: III. EFFECT OF HEAT ON CASEIN, LACTALBUMIN, AND THEIR LACTOSE-INDUCED DERIVATIVES, WITH SPECIAL REFERENCE TO DIGESTIBILITY AND RATE OF RELEASE OF LYSINE, METHIONINE, AND TRYPTOPHAN. BESSIE B. COOK, JANE FRAENKEL-CONRAT, BEATRICE SINGER, and AGNES FAY MORGAN, J. Nutrition **44**:217 (June 11) 1951.

The effects of heat or lactose or both on casein and several types of lactalbumins have been investigated. It was noted that mild lactose treatment did not significantly decrease the rate of digestion or the release of any of the amino acids measured at the end of 24 hours. There was a decrease in total available amino acids when digestion was carried on for 72 hours. Heat at 118 C. for 30 minutes in addition to mild lactose treatment altered significantly the rate both of digestion and of release of amino acids; heat at 150 C. for 70 minutes intensified these differences. Heat alone also exercised a delaying action on the release of the amino acids measured. Inasmuch as the amino acids of the various protein-lactose derivatives and their heated products are not released at the same rate, it may be suggested that the loss of biological value of these modified proteins is due to absorption of their respective amino acids by the intestine at rates which will not allow for mutual supplementation.

FREDEEN, Kansas City, Mo.

CLINICAL ASPECTS OF THE SYNDROME OF TOXICOSIS IN INFANTS. G. BELLIENI, Minerva pediat. **3**:635 (Nov. 15) 1951.

The clinical aspects of toxicosis as described by 40 different authors are charted. The conclusion is drawn that the diagnosis of toxicosis in infants is dependent, not on any given symptom, but rather on the simultaneous appearance of many symptoms.

HIGGINS, Boston.

THE FEEDING OF EGGS TO INFANTS. G. ZARBIN and R. ARESI, Minerva pediat. **4**:571 (July 31) 1952.

Twenty-four of 113 infants, 4 to 7½ months old, had upsets—vomiting, diarrhea, or urticaria—following their initial feeding of egg. Vomiting was the commonest disturbance in the breast-fed infants, and urticaria in the bottle-fed infants. Of the 4-month-old infants, 35% had upsets; the percentage had fallen to 12.5% among the 6½ to 7½ month-old infants. The recommendation is made that egg yolk not be fed to infants until they are at least 6 months old.

HIGGINS, Boston.

TREATMENT OF ALIMENTARY INTOXICATION OF INFANTS. WERNER DROESE and ERICH ROMINGER, Med. Klin. **45**:324 (March 17) 1950.

Theoretical considerations led to the following regimen in cases of alimentary intoxication of infants. A stomach lavage with Ringer's solution is followed by the administration of 2 teaspoonful of animal charcoal in a little Ringer's solution by stomach tube. Four hours later 10 to 15 ml. of castor oil is given. During the first 24 hours tea is given exclusively, in some cases with 100 to 150 cc. of Ringer's solution. Five to 10 mg. of desoxycorticosterone in aqueous solution is injected intravenously or 5 mg. of an oil-soluble preparation is given by intramuscular injection. The dose is determined by the weight of the child and the degree of intoxication. Increasing the volume of circulating blood by injection of plasma or of 5% dextrose-Ringer solution is done only in special cases. On the second day the fluid requirements are met by a bottle of carrot juice with 5% sugar (a mixture of dextrose and fructose). The daily sugar intake must not exceed 30 to 40 gm. If Ringer's solution is still needed, the amount is reduced to 50 to 100 cc. In especially severe cases 5 mg. of oil-soluble desoxycorticosterone acetate is given. On the third day if the child is no longer toxic, 50 to 100 cc. of serum is added to the diet of the preceding day; the amount of serum depends on the age and weight of the child. On the next day the amount of serum is increased to 150 to 200 cc. On succeeding days the serum is gradually replaced by buttermilk powder (mother's milk was not available to the authors). A detailed report of the clinical and experimental investigations will be published elsewhere.

AMBERG, Rochester, Minn.

SOME NEW DIETETIC PREPARATIONS FOR INFANTS. J. KEYZER and M. MANDERS, Maandschr. kindergeneesk. **17**:336, 1950.

The first communications from Moro and Pfaundler regarding carrot soup are recalled. During the recent war communications from German authors revived interest in this remedy. Keyzer and Manders experimented with a carrot powder prepared by a Dutch firm, with favorable results. They warn against its continued use for very young infants and describe two cases of obstruction caused by it.

The effect of Arobon, manufactured from the pulp of carob beans, is less strong. In certain cases (especially those of young infants) Arobon is preferable as an astringent in the treatment of diarrhea.

A description is given of three cases of habit vomiting and rumination in which the addition of 1% of thickening powder (Nestargel) (prepared from the seeds of the carob beans) to the feeding immediately controlled the vomiting. The infants promptly increased in weight. The great advantage of Nestargel is that the feeding need be changed neither quantitatively nor qualitatively and that the prepartion can be easily used without hospitalization.

FROM THE AUTHORS' SUMMARY.

Hygiene; Growth and Nutrition; Public Health

MORTALITY FROM VIOLENCE IN CHILDHOOD IN AUSTRALIA. F. W. CLEMENTS, M. J. Australia **2**:654 (Nov. 8) 1952.

A study of mortality rates from accidents in childhood reveals that traffic accidents are most important in the three age groups 1 to 4 years, 5 to 9 years, and 10 to 14 years. Poisoning is important in the 1 to 4 year group, while drowning is important in all groups. Future reduction of childhood mortality rates will depend on a considerable reduction in all forms of accidental death.

MCGUIGAN, Evanston, Ill.

DEVELOPMENT CURVES AND DEVELOPMENT TYPES. A. KALLNER, Ann. pædiat. **177**:83 (Aug.) 1951.

Wetzel's method (grid) of recording the development of healthy children is scrutinized in the light of weights and measures which have been taken during a period of 15 years and is compared with an older method of depicting development which gives a better picture of the changes in length and weight. The retrospective investigation of individual curves over a

number of years, probably a longer period than that observed by the American authors, shows that developmental deviations which, if tested with the grid method, appear to be pathological, are not at all rare and may therefore easily lead to diagnostic, prognostic, and therapeutic errors. The results of the grid method, on the other hand, are of great importance, as they tend to widen our biological knowledge. For the work of the physician in an individual case they have to be used with great caution. In any case it is impossible when using the grid method to give a prognosis with regards to further development.

FROM THE AUTHOR'S SUMMARY.

UNIFIED HEALTH SERVICE IN ROUMANIA. M. SVEJNAROVA-POHLOVA, Pediat. listy **7**:358 (Dec.) 1952.

An account is given of the results achieved so far by the unified Health Service in Roumania, based on personal observation and information gathered during a stay in that country.

FROM THE AUTHOR'S SUMMARY.

Prematurity and Congenital Deformities

STUDIES OF THE IMMUNOLOGY OF THE NEWBORN INFANT: III. PERMEABILITY OF THE PLACENTA TO MATERNAL ANTIBODY DURING FETAL LIFE. JOHN J. OSBORN, JOSEPH DANCIS, and BLANCHE V. ROSENBERG, Pediatrics **10**:450 (Oct.) 1952.

The titer of diphtheria antitoxin in maternal and infant (cord) blood was compared in 56 premature infants. A significant correlation was found between birth weight and placental permeability to diphtheria antitoxin. Small premature infants (under 1,200 gm.) have much less circulating antitoxin derived from the mother than do larger premature infants.

In 10 premature infants with high cord titers of diphtheria antitoxin, this passive immunity was lost at about the same rate as by normal newborn infants.

FROM THE AUTHORS' SUMMARY.

ELECTROPHORETIC ANALYSIS OF SERUM PROTEINS IN PREMATURE INFANTS. PATRICIA M. NORTON, HANS KUNZ, and EDWARD L. PRATT, Pediatrics **10**:527 (Nov.) 1952.

Forty-four measurements of the concentrations of total serum protein determined by a Kjeldahl procedure and of albumin and alpha$_1$, alpha$_2$, beta, and gamma globulins determined electrophoretically in the serum of 27 premature infants ranging in age from 7 hours to 65 days are reported.

Wide variations in all values are evident in individual cases. Certain trends are, nevertheless, apparent. During the first five to six weeks there is a gradual decline in the concentrations of total serum protein, albumin, and gamma globulin. The alpha and beta globulins show no trend with age in this study.

Except for slightly higher values for alpha$_1$ globulins in the smaller infants, none of the concentrations could be correlated with the birth weights of the patients.

FROM THE AUTHORS' SUMMARY.

DEHYDROEPIANDROSTERONE AND SIMILAR SUBSTANCES IN URINE OF PREMATURE INFANTS. J. FREDERICK EAGLE, Proc. Soc. Exper. Biol. & Med. **81**:571 (Dec.) 1952.

The "blue test" for dehydroepiandrosterone and other closely related compounds has been found to be positive 10 times in 11 patients with adrenal tumor; in 15 patients with congenital adrenal hyperplasia the test was always negative. The authors studied this test in relation to prematures and infants under one year with no evidence of adrenal tumor. It was found that the urine of 9 out of 18 premature infants yielded a positive "blue test." Of four infants found to have negative responses when tested at least three times, two had both positive and negative tests. There were 66 examinations of the urine of the 18 infants, and the "blue test" was positive 24 times. There was no correlation among age, weight, diet, medication, time of day, or any stress factors, or the total amount of 17-ketosteroids in the urine. In 18 examinations of the urine of 15 patients under one year of age (not premature) the test was positive once in

2 patients. It is felt that the main compound giving the blue color is dehydroepiandrosterone. The authors conclude that the test cannot be used to differentiate between an adrenal tumor and benign hyperplasia in premature infants and must be interpreted with caution in children under one year of age.

HANSEN, Galveston, Texas.

HEREDITARY TRANSMISSION OF PHYSICAL DEFECTS IN THE EMB FAMILY. E. R. SELBY, Canad. M. A. J. **66**:439 (May) 1952.

Similar physical anomalies occurring in four successive generations of a family are discussed. The anomaly concerned deformities of both hands and feet. In the entire series, no apparently physically normal person produced a deformed offspring, while the deformity was transmitted and inherited by both males and females alike. The author points out the advantage of legal sterilization in families such as this.

MCGUIGAN, Evanston, Ill.

PATHOLOGY AND BIOCHEMISTRY OF GARGOYLISM. J. L. HENDERSON, AGNES R. MACGREGOR, S. J. THANNHAUSER, and R. HOLDEN, Arch. Dis. Childhood **27**:230 (June) 1952.

Three cases of gargoylism are recorded. An extensive study of the pathology and biochemistry in one case was made. Biopsy specimens in the other two cases were examined histologically and in one of these also biochemically. The gross vascular and meningeal pathology was a notable feature in the case which came to necropsy. These features had not been described before but have since been observed by others.

The literature relating to the pathology and biochemistry is reviewed in detail.

The pathogenesis of the disease remains unproved. The intracellular deposit is neither a lipid nor glycogen. Further biochemical studies should demonstrate whether the substance is a glycoprotein or mucoprotein, as has been suggested.

FROM THE AUTHORS' SUMMARY.

METHYL TESTOSTERONE IN PREMATURE INFANTS. URSULA JAMES and B. L. COLES, Arch. Dis. Childhood **27**:265 (June) 1952.

No significant difference in the time taken to regain birth weight or the amount of weight gained over birth weight at the age of one month was noted between the treated infants and the controls in any weight group.

No side-effects were noticed as a result of treatment apart from the transient enlargement of the clitoris in two cases.

The authors believe it unlikely that the normal adequately nourished premature infant responds to the growth stimulus of testosterone, and in their opinion this hormone is of no value in the rearing of healthy premature babies.

KELLY, Milwaukee.

PATHOGENESIS OF MULTIPLE MALFORMATIONS. O. MALAGUZZI-VALERI and ANTELIO FICARI, Arch. ital. pediat. e puericolt. **14**:247, 1951.

A case is reported of various abnormalities—congenital stenosis of the duodenum, dilatation of the esophagus, pulmonary cysts, and bronchiectasis—and the pathogenesis is discussed.

The duodenal malformation is characterized by an iris-like septum in the duodenojejunal junction which is formed by mucosa, submucosa, and muscullaris mucosae. The esophageal dilatation is definitely megaesophagus. The cysts of the lungs and the bronchiectasis could be explained as due to the same pathogenetic mechanism, since the histologic findings show almost total absence of elastic tissue in the lung parenchyma and in the bronchial wall. The gaseous cysts could be referred to the dilatation of the terminal bronchioles, alveolar channels, and alveolae.

The pathogenetic correlation between these various abnormalities are examined. The probable phase of the embryonal life is discussed in which the pathogenetic agents could have determined the disturbances of embryonic development. Since the malformation in the present instance are observed in the organs which arise from the primitive gut, the hypothesis is considered that the teratogenetic agents could have influenced the primitive gut when the various organs had not yet differentiated.

FROM THE AUTHORS' SUMMARY.

A Case of Gargoylism (Hurler's Disease). S. Li Moli, Minerva pediat. **4**:544 (July) 1952.

Examination of a 4-year-old girl revealed the typical findings of Hurler's disease: dwarfism, grotesque facies, enlarged sella turcica, cloudy cornea, kyphosis, enlarged liver and spleen, umbilical hernia, rigid joints, hypertension, and mental retardation. Gargoylism, or Hurler's disease, is now recognized as a storage disease, probably storage of a glycoprotein.

Higgins, Boston.

Newborn

Valvular Thrombotic Vegetation in Newborn ("Fetal Endocarditis"). Richard H. McDonald, Arch. Path. **50**:538 (Nov.) 1950.

A case of a fresh vegetation occurring on a cardiac valve in a newborn infant is presented. It is the third case accompanied by histological data to be recorded in the literature. Despite maternal syphilitic infection, syphilis is not considered of etiologic importance since adequate antepartum treatment was given and no lesions suggestive of that disease were encountered. The etiology of the valvular lesions is not clear. The author suggests that the vegetation may represent a bland thrombus forming on surface irregularities concerned in the development of valvular hematomas, or as a result of hypothetical rupture of one of these blood cysts found on the cardiac valves of the newborn. Other explanations follow those given by Allen and Sirota, who have described identical lesions under the label "degenerative verrucal endocardiosis." These authors considered allergy, ascorbic acid deficiency, and homodynamic trauma of thickened valves as possible causes.

Haw Chan, San Francisco.

Development of Neonatal Electrolyte Homeostasis. B. D. Graham, J. L. Wilson, M. U. Taso, Mary L. Baumann, and Shirley Brown, Pediatrics **8**:68 (July) 1951.

Data were collected to compare capillary blood levels for the following factors during the first day of life of normal newborn infants: blood pH, plasma CO_2, chloride, total base, total serum proteins, and, by subtraction, the "R" component in the Gamble diagram.

This group is also compared with a group of premature infants previously reported and with a normal adult control group.

Most full-term infants at birth are in a state of metabolic acidosis with a lowered blood pH and plasma CO_2 content, but have essentially normal plasma chlorides and total base values. The majority of these infants within a few hours have a blood pH of adult level but maintain for some time a lowered CO_2 content.

Blood O_2 content, capacity, and percentage saturation were also determined, and comparison was made between the technics of delivery, i. e., deliveries by saddle-block and caudal analgesia and deliveries with ether or nitrous oxide anesthesia. No great difference in O_2 saturation was noted when these four groups were compared, either at birth or subsequently during the first day of life.

From the Authors' Summary.

Blood Sugar and Citric Acid Levels in Newborn Infants. Isaac F. Gittleman and Joseph B. Pincus, Pediatrics **9**:38 (Jan.) 1952.

Citric acid levels of 161 newborn infants varying in age from 2 hours to 8 days were determined. All infants were on a diet of evaporated milk with 5% Dextri-Maltose. The highest levels were found in the youngest subjects. The citric acid values varied between 0.5 and 5.5 mg. per 100 cc.

Glucose levels of 151 of the same infants were also determined, and the authors found a tendency for the sugar levels to rise as the infants advanced in age.

A relationship between citric acid and glucose metabolism is again suggested by this study.

From the Authors' Summary.

UNILATERAL PARALYSIS OF THE DIAPHRAGM IN THE NEWBORN INFANT DUE TO PHRENIC NERVE INJURY, WITH AND WITHOUT ASSOCIATED BRACHIAL PALSY. NATHAN SCHIFRIN, Pediatrics **9**:69 (Jan.) 1952.

Four infants with unilateral paralysis of the diaphragm in the newborn period due to phrenic nerve injury are presented. In two infants there was no concomitant brachial plexus involvement. In one infant, transient unilateral vocal-cord paralysis was noted. The presenting symptom in all infants was respiratory difficulty. Fluoroscopic examination of the chest in addition to roentgen examination is urged for all infants with respiratory difficulty in the newborn period.

FROM THE AUTHOR'S SUMMARY.

FUNCTION OF THE ADRENAL GLANDS IN THE NEWBORN. B. WOLMAN, Arch. Dis. Childhood **27**:283 (June) 1952.

Corticotropin (ACTH) was given to 24 full-term and 12 premature newborn infants, and the changes in circulating eosinophiles were measured.

Sixteen of the full-term and four of the premature infants showed a normal response, as shown by a 50% decrease in eosinophiles on the first day of life. All but two of the others showed a normal response on the second day of life.

One baby, whose birth weight was 5 lb. 12 oz. (2,600 gm.) responded on the third day, but an infant born of a diabetic mother did not give a normal response till the end of the first week.

It is concluded that, although the adrenal cortex is anatomically immature in the first days of life, its function is normal in the majority of newborn and premature infants on the first day and in the rest on the second day of life.

KELLY, Milwaukee.

SPONTANEOUS RUPTURE OF THE HEART IN THE NEWBORN INFANT. W. E. HUNT, Arch. Dis. Childhood **27**:291 (June) 1952.

A case is reported of a stillbirth in which fetal death was caused by spontaneous perforation of the right atrium with subsequent hemopericardium, shortly before delivery. The rupture occurred at a point where the atrial myocardium had undergone focal hyaline degeneration, no cause for which was found.

This is believed to be the second recorded case of spontaneous hemopericardium occurring in the newborn infant and the first in which this lesion has been the cause of stillbirth.

KELLY, Milwaukee.

THREE CASES OF CEPHALHEMATOMA IN THE NEWBORN. A. GIANELLI, Minerva pediat. **3**:591 (Nov. 1) 1951.

A child had had a cephalhematoma following birth; it had not been absorbed. When the child was seen at the age of 10 years, there was still a hard bony swelling over one parietal bone. At the request of the parents, this bony swelling was removed for cosmetic reasons.

Whereas there had been a high mortality rate (60%) among infants following an operation for cephalhematoma in the preaseptic era of surgery, the practice developed of letting the swelling be absorbed without intervention; this procedure has continued to the present time. Giving the baby an injection of vitamin K after detection of the cephalhematoma has usually led to its rapid absorption. Aspiration may be done if the cephalhematoma is not being absorbed after some weeks, but no sclerosing material should be injected nor should the skin be incised or traumatized.

HIGGINS, Boston.

Acute Contagious Diseases

VARICELLA PNEUMONITIS: REPORT OF A CASE WITH AUTOPSY OBSERVATIONS. LESTER FRANK, Arch. Path. **50**:450 (Oct.) 1950.

Deaths due to chicken pox are rare and a survey of the literature reveals an even greater rarity of autopsy reports of these cases. This paper is concerned with the autopsy observations in a case of varicella in a 34-year-old woman who died in the acute phase of the disease. Varicella was epidemic in the area, but no other deaths had been reported. Gross findings of

greatest significance were the skin lesions, which were discrete, present in decreasing order of frequency on the face, neck, upper torso, lower torso, arms, thighs, and forearms. They appeared as reddish-purple papules, large nonumbilicated vesicles, measuring up to 1 cm. in their largest diameter, and ruptured vesicular lesions, many with a hemorrhagic base. The vesicles were located entirely on the neck. Numerous ulcers, measuring up to 1 cm. in diameter with a necrotic base, covered the entire length of the esophagus. Microscopic section of the skin lesions showed localized areas of alteration involving the epithelium and sometimes including the entire thickness of the dermis. Cells containing large intranuclear inclusion bodies were present. The changes in the lungs microscopically were those usualy seen in other types of virus pnuemonia, with the addition of characteristic intranuclear inclusion bodies in the septal cells and bronchiolar epithelial cells. No inclusion bodies were found in any other epithelial cells besides the skin and lungs.

HAW CHAN, San Francisco.

AUREOMYCIN TREATMENT OF PERTUSSIS: RESULTS IN 137 PATIENTS. PAUL F. WEHRLE and MARK H. LEPPER, J. Pediat. **39**:435 (Oct.) 1951.

In this series of 137 treated patients, aureomycin did not affect the course of pertussis. It did markedly lower the incidence of secondary complications.

MACDONALD, Pittsburgh.

POLIOMYELITIS AND COXSACKIE VIRUSES ISOLATED FROM NORMAL INFANTS IN EGYPT. JOSEPH L. MELNICK and KARIN ÅGREN, Proc. Soc. Exper. Biol. & Med. **81**:621 (Dec.) 1952.

Poliomyelitis has been rarely reported in Egypt, yet neutralizing antibodies for all three types of the disease have been found in the sera of three-fourths of the native infants before they reach 4 years of age. Rectal swabs, 36 in all, were collected from normal babies between 6 and 12 months of age in the region of Cairo. One strain of poliomyelitis virus, nine of Coxsackie virus, and an unknown agent were isolated.

HANSEN, Galveston, Texas.

POLIOMYELITIS IN EARLY INFANCY. CAREY W. PHILLIPS JR. and J. DEAN PASCHAL, South. M. J. **45**:1054 (Nov.) 1952.

The authors report the case of a white boy in whom signs of poliomyelitis developed on the 14th day of life. The diagnosis was confirmed at necropsy.

LOGAN, Rochester, Minn.

POLIOMYELITIS AND ALLERGY. F. DRAPER and GRACE FORDHAM, Clin. Rep. Adelaide Child. Hosp. **2**:117 (Nov.) 1951.

An attempt to correlate the incidence of poliomyelitis with a history of allergy in the families showed that poliomyelitis occurs with increased frequency in allergic families and that this increase is statistically significant.

MCGUIGAN, Evanston, Ill.

LEG SIGNS IN POLIOMYELITIS. GUIDO NOCCIOLI, Riv. clin. pediat. **50**:753 (Nov.) 1952.

The author describes leg signs which can be utilized especially in the study of children with poliomyelitic paralysis.

FROM THE AUTHOR'S SUMMARY.

Acute Infectious Diseases

PATHOLOGY OF OXYURIASIS. W. ST. C. SYMMERS, Arch. Path. **50**:475 (Oct.) 1950.

It is generally accepted that oxyuriasis (enterobiasis) is the most prevalent of the worm infections which occur in man, yet descriptions of pathological changes associated with the presence of threadworms (pinworms) are comparatively uncommon. Oxyuriasis only exceptionally causes pathologic changes in the tissues; it is not a significant cause of appendicitis; nevertheless, it can on rare occasions alone produce important changes. A general review of the biology of the worm, concepts as to the manner and source of infection, prevalence, symptoms, and pathogenicity is given.

The author then presents three cases of oxyuris granuloma in detail. One case is that of a 13½-year-old boy who underwent a nephrectomy. The remains of a gravid oxyurid were found in the ureter of the atrophic kidney. This finding appears to be the first record of the presence of this parasite in the kidney or ureter.

HAW CHAN, San Francisco.

CAT-SCRATCH FEVER. H. L. LANGE, J. Pediat. **39**:431 (Oct.) 1951.

Cat-scratch fever is characterized by (1) a history of scratch by a house cat; (2) an incubation period of one week or less; (3) a red papule appearing at the site of scratch and accompanied by irregular fever lasting four or five days; (4) appearance about one day later of regional lymphadenitis, which may become suppurative (generalized lymphadenopathy may occur); (5) leucocytosis with shift to the left early in the disease; (6) negative agglutination and skin tests for tularemia and brucellosis, and (7) recovery in three weeks to two months.

In these three cases, chloramphenicol or terramycin seemed to be most effective.

MACDONALD, Pittsburgh.

INFECTIOUS LYMPHOCYTOSIS: A REPORT OF 2 CASES NOTED FOLLOWING TRAUMA. SYDNEY WALDMAN and ABRAHAM M. FRUMIN, J. Pediat. **39**:455 (Oct.) 1951.

Waldman and Frumin report two cases of infectious lymphocytosis following trauma.

MACDONALD, Pittsburgh.

RHEUMATOID ARTHRITIS AND AMEBIASIS. ROBERT E. RINEHART, Northwest Med. **51**:225 (March) 1952.

One hundred one consecutive patients with rheumatoid arthritis and 15 consecutive patients with rheumatoid spondylitis were examined for infection with Endamoeba histolytica. The age of the patients ranged from 4 to 76 years. Ninety-two per cent of those with rheumatoid arthritis and 87% of those with rheumatoid spondylitis were found to be infected. Ten stool specimens were sent to the United States Public Health Service for confirmation of the diagnosis. Findings agreed completely with those of the author's laboratory.

"Improvement and at times complete remission of the rheumatoid state was noted when the amoebic infection was successfully treated. The findings strongly suggest an etiological relationship between most cases of rheumatoid arthritis and infection with endamoeba histolytica."

FROM THE AUTHOR'S SUMMARY.

LABELED METHIONINE AS AN INDICATOR OF PROTEIN FORMATION IN CHILDREN WITH LIPOID NEPHROSIS. VINCENT C. KELLEY, MILDRED R. ZIEGLER, DORIS DOEDEN, and IRVINE MCQUARRIE, Proc. Soc. Exper. Biol. & Med. **75**:153 (Oct.) 1950.

Four children, 2 to 7 years of age, with nephrosis and two control subjects, 1½ to 6 years, were given intravenously 20 ml. of saline solution containing methionine labeled with S^{35}. Blood specimens were obtained 5 hours and 24 hours later. The results, expressed as the "biological concentration coefficient," disclosed remarkably close values for the control subjects, whereas in striking contrast distinctly higher (two and-half to five and-half times) values were obtained in the nephrotic patients. The authors state that the rate of serum protein formation would appear to be greater in nephrotic patients than in control patients, although further investigations are in order.

HANSEN, Galveston, Texas.

GONOCOCCAL VULVOVAGINITIS IN INFANTS AND CHILDREN: A STUDY OF 240 CASES. CHUNILAL MUKHERJEE, Arch. Dis. Childhood **25**:262 (Sept.) 1950.

Gonorrhea accounts for probably not more than half the cases of vulvovaginitis in infants and children. Estrogens, penicillin, and sulfonamides cannot offer an absolute assurance of cure. No matter what treatment is employed, a certain number of cases appear to be resistant. With estrogens a 72 to 75% cure rate is about the average which can be expected. With penicillin and sulfonamides, a 90% recovery rate is a modest expectation. A comparative study of the results obtained with these three therapeutic measures is tabulated.

The difference between results obtained with sulfonamides and with penicillin is not striking. Sulfonamides, however, possess some toxicity, and therefore sulfonamide-treated patients require to be watched carefully. The duration of treatment is about the same with the two types of

drugs. Penicillin is at present expensive, and the frequent medication necessarily is a drawback. The results of local penicillin treatment have been very encouraging and can be depended upon if the parents can cooperate.

Estrogens also possess a distinct place in the treatment of vulvovaginitis. With the use of synthetic drugs expense is not a serious problem, but the course of treatment is prolonged and the recovery rate lower than with either sulfonamides or penicillin. The value of estrogen therapy is, however, considerably increased in the treatment of patients with relapse or with refractory infections. It is in these that the combination of estrogens with either sulfonamide or penicillin is almost always rewarded with success.

FROM THE AUTHOR'S SUMMARY.

GANGRENOUS PURPURA AND ITS OCCURRENCE IN MENINGOCOCCAL SEPTICAEMIA. H. G. DUNN, Arch. Dis. Childhood **26**:192 (April) 1951.

The occurrence of gangrenous purpura with recovery in an infant aged 4½ months is described.

The etiology of the condition is discussed. It is concluded that gangrenous purpura is not a disease sui generis but may have a number of known causes, though an idiopathic, possibly anaphylactoid, form is still reported. Among the recognized causes septicemia now appears the commonest, particularly that due to meningococcal infection. This was held responsible in the case described.

It is pointed out that the apparently primary forms of gangrenous purpura (purpura gangraenosa) have a similar etiology to that of purpura fulminans and that the former may often develop from the latter, particularly if specific therapy is applied.

The features of gangrenous purpura in meningococcal septicemia are discussed in detail. Sensitization as in the Shwartzman phenomenon may play a part in the pathogenesis of the vascular lesions which are responsible for the purpura in this disease. Such a mechanism may form a connecting link among the severe types of purpura with necrosis in various conditions.

KELLY, Milwaukee.

ABDOMINAL MANIFESTATIONS OF RHEUMATIC FEVER. A. RANIERI, Ann. ital. pediat. **3**:278, 1950.

The author reports on nine cases of abdominal disorders preceding a recurrence or relapse of rheumatic infection. He describes the clinical manifestations and refers their origin to an early rheumatic infection localization in the peritoneum, which would manifest a more or less severe pain.

FROM THE AUTHOR'S SUMMARY.

ANTIGENS OF EBERTH'S BACILLI CULTURED FROM PATIENTS UNDERGOING VARIOUS METHODS OF TREATMENT. L. BAVASTRELLI, Minerva pediat. **3**:579 (Nov. 1) 1951.

Cultures of typhoid bacilli were obtained from the blood, the bone marrow, and the feces of 20 patients undergoing treatment with (1) chloramphenicol or (2) vaccine and high protein feeding.

The clinical course of the patients was the same, regardless of the treatment employed. Chloramphenicol therapy led to a more rapid disappearance of the typhoid bacilli from the blood and the feces but not from the bone marrow.

The amounts of antigens O and H in all the cultures and of antigen Vi, except in a few cultures from the bone marrow, were not changed by the type of therapy given or by the clinical severity of the typhoid fever.

HIGGINS, Boston.

SOLITARY CYST OF THE KIDNEY IN A SIX-YEAR-OLD BOY. A. RIGHINI, Riv. clin. pediat. **48**:663 (Oct.) 1950.

The author, after some clinical considerations of the literature already existing on the subject (such anatomopathological forms being rare in pediatric surgery), describes a case of solitary cyst of the kidney in a 6-year-old child. He also describes the histologic examination of the removed portion and the preoperative and postoperative urography.

FROM THE AUTHOR'S SUMMARY.

Chronic Infectious Diseases

PRESENT STATUS OF THE CHEMOTHERAPY OF TUBERCULOSIS WITH CONTEBEN, A SUBSTANCE OF THE THIOSEMICARBAZONE SERIES. ANTON MERTENS and ROLF BANGE, Am. Rev. Tuberc. **61**:20 (Jan.) 1950.

From Germany has come the report of the results of the treatment of more than 10,000 patients with tuberculosis in various forms and stages with the chemotherapeutic agent designated amithiozone (thiosemicarbazone; Conteben). Among the claims made for this agent are the following: Results in pulmonary tuberculosis associated with a perifocal inflammatory process are favorable; the more active the process, the more promising is the therapy. Miliary tuberculosis and tuberculous meningitis are not satisfactorily controlled.

Cavernous processes respond very favorably to oral administration of amithiozine and intracavernous treatment promises success even in severe progressive processes. Most favorable results are obtained in tuberculous disease of the mucous membranes, such as tracheobronchitis, bronchitis, and laryngeal, intestinal and bladder tuberculosis. In renal tuberculosis, preliminary reports are encouraging. The response of bone and joint tuberculosis cannot as yet be determined.

The dosage of amithiozone must be strictly individualized and adapted to the form and stage of the tuberculous process and response to treatment.

Toxic effects have been observed, involving the digestive systems, skin, and blood, but these reactions are reported to be of less frequent occurrence and to be less serious with increasing experience in the use of the drug. Certain disturbances of liver function are encountered which will require further study.

EUGENE SMITH, Ogden, Utah.

AMERICAN TRUDEAU SOCIETY: REPORT TO CLINICAL SUBCOMMITTEE ON GERMAN EXPERIENCES WITH AMITHIOZONE (THIOSEMICARBAZONE). H. CORWIN HINSHAW and WALSH MCDERMOTT, Am. Rev. Tuberc. **61**:45 (April) 1950.

This paper should be read in connection with other papers by German authors in this issue. There are reported to be more than 300 hospitals and sanatoriums participating in the clinical trials of amithiozone (thiosemicarbazone: Conteben) and it was estimated that more than 7,000 patients had received treatment with this drug. The authors visited numerous hospitals in the Western Zones of Germany and conferred with physicians and surgeons with various interests in different aspects of the problem under study. As a result of these observations, the authors conclude that amithiozone is not a sufficiently powerful antituberculosis drug to exert a significant influence on most instances of miliary and meningeal tuberculosis.

Other types of clinical tuberculosis found most responsive to antituberculosis drugs in America appear to have responded to amithiozone therapy in Germany. Especially notable are the results of its use in the more superficial but very serious types of mucous membrane complications of extensive pulmonary tuberculosis, especially tuberculous laryngitis and tuberculous enteritis.

Pulmonary tuberculosis treated before irreversible changes have developed probably responds to amithiozone therapy, but doubt remains as to whether it is preferable to streptomycin. In extrapulmonary tuberculosis the evidence is somewhat confusing, but alone or in combination with other drugs conteben may prove to be a valuable adjunct in treatment.

Amithiozone has a potential toxicity which seems to be definitely greater than that of either streptomycin or paraaminosalicylic acid. However, there is reason to believe that with proper caution it may be given over long periods without undue risks.

Amithiozone appears to have an antituberculosis activity of approximately the same general order as paraaminosalicylic acid and a potential toxicity somewhat like that of the arsenicals used in syphilis.

It is virtually certain that amithiozone could not replace streptomycin but could be used together with streptomycin in the treatment of tuberculosis.

EUGENE SMITH, Ogden, Utah.

STREPTOMYCIN AND PROMIZOLE IN THE TREATMENT OF WIDESPREAD PULMONARY TUBERCULOSIS IN A 19-DAY-OLD INFANT. EDWIN L. KENDIG JR. and FRANKLIN L. ANGELL, Am. Rev. Tuberc. **61**:747 (May) 1950.

The baby of a mother known to have sputum positive for tubercle bacilli was "born into the toilet" at home 10 hours prior to its admission to the hospital. Examination at the hospital revealed an apparently normal premature infant who weighed 2,268 gm. The baby was apparently making normal progress with satisfactory gain in weight on the 19th day of age, when the temperature was recorded at 100.8 F. On the same day a roentgenogram of the baby's chest showed very fine miliary mottling throughout both lungs. A Mantoux test (0.001 mg. of old tuberculin) was positive, and when the infant was 25 days old tubercle bacilli were demonstrated by direct smear and culture of gastric contents. Spinal fluid examination showed 15 cells, of which 11 were lymphocytes and 4 were polymorphonuclears; protein was 104 mg. and sugar 46 mg. per cubic centimeter and chlorides 86 mEq. per liter. No acid-fast organisms were ever demonstrated in the spinal fluid by smear, culture, or guinea pig inoculations. Treatment instituted consisted of streptomycin given intrathecally, 25 mg. every two days for approximately three months, and streptomycin given intramuscularly in a dose of 30 to 40 mg. per pound of body weight. At one time, when the baby was 4 months old, use of streptomycin was temporarily discontinued and thiazolylsulfone (Promizole) was given. The administration of streptomycin was resumed in one month. For three months progressive involvement of the lungs was shown by x-ray, but at the end of this time diminution in the mottling was noted; shortly thereafter a nodule suggestive of a well-defined Ghon complex was noted. One year from the date of admission the roentgenogram showed a healed primary focus and a group of hilar nodes with linear fibrosis in the right lung. The left lung was clear.

The authors believe that this was not a case of congenital tuberculosis but that in some manner the infant became infected during the short space of time it was in contact with the mother. At 19 months of age the patient showed no clinical sign of active tuberculous infection.

EUGENE SMITH, Ogden, Utah.

A PARTIALLY HEALED PRIMARY LESION IN A CASE OF GENERALIZED HISTOPLASMOSIS. DALE M. SCHULZ, Arch. Path. **50**:457 (Oct.) 1950.

A case of a 6-month-old white boy is presented. There was a history of four months of illness with rapid progression to death associated with liver and spleen enlargement in the last two months of life. At autopsy disseminated histoplasmosis was found. The most striking features, however, were partially calcified caseous nodules found in the lung and a tracheobronchial lymph node analogous to the primary complex of tuberculosis. This case gives anatomical evidence that Histoplasma may enter the body by the respiratory tract and produce primary lesions in the lung and draining lymph nodes, which may heal with calcification.

HAW CHAN, San Francisco.

FAILURE OF ACTH OR CORTISONE TO SUPPRESS TUBERCULIN SKIN REACTIONS IN TUBERCULOUS GUINEA PIGS. WALTER H. SHELDON, MARTIN M. CUMMINGS, and LILIAN D. EVANS, Proc. Soc. Exper. Biol. & Med. **75**:616 (Nov.) 1950.

Fifteen male albino guinea pigs were found to be tuberculin-negative. The animals were then inoculated with 0.1 mg. of a young culture of human virulent tubercle bacilli. One month later the animals were divided into three groups: Five animals received daily injections of 2 mg. of corticotropin (ACTH) intramuscularly, another five received subcutaneous injections twice daily with 2 mg. of cortisone acetate, and the remaining five animals served as controls. On the fourth day of hormone administration the tuberculin tests were repeated. A definite tuberculin skin reaction was obtained in all animals during the period of hormone administration. The reaction appeared less marked in the treated animals than in the controls. It is suggested that corticotropin (ACTH) and cortisone do not interfere primarily with the immune mechanism of the tuberculin skin reaction but decrease the associated acute inflammatory process.

HANSEN, Galveston, Texas.

THIACETAZONE IN PULMONARY TUBERCULOSIS. J. H. ROLLAND RAMSAY, Edinburgh M. J. **58:** 29 (Jan.) 1951.

Amithiozone paraacetylaminobenzaldhyde thiosemicarbazone (thiacetazone) is an antituberculosis drug developed in Germany in the latter years of the last war. It is ineffective against tuberculous meningitis and miliary tuberculosis. However, it has been claimed that the drug is valuable in treatment of tuberculosis of the larynx and intestine. Ramsay treated 11 patients with pulmonary tuberculosis with the drug. Digestive disorders, anemia, and evidences of liver damage due to amithiozone were observed. The beneficial effects of the drug were not striking, and the author concludes that amithiozone, potentially more dangerous than *p*-aminosalicylic acid or streptomycin, is, by comparison, less effective in the treatment of tuberculosis.

MACDONALD, Pittsburgh.

PULMONARY TUBERCULOSIS IN CHILDREN. R. SACREZ and G. BURGHARD, Pédiatrie **40:**9, 1951.

This entire issue is devoted to a report of the meeting on pulmonary tuberculosis in children in Strasbourg. The five main reports deal with (1) the treatment and immediate prognosis of primary pulmonary tuberculosis in children; (2) the transition of primary tuberculosis into chronic tuberculosis in older children and adolescents; (3) general considerations of breathing disturbances in children; (4) nontuberculous breathing disturbances in children, and (5) roentgenological findings in breathing disturbances in children.

The rest of the issue is devoted to shorter reports on related subjects.

GLASER, Jerusalem.

CALCIFIED MILIARY TUBERCLES: REPORT OF A CASE OF DIFFUSE PULMONARY MICROCALCIFICATIONS, SEQUELAE OF ACUTE MILIARY TUBERCULOSIS TREATED WITH STREPTOMYCIN. P. BERTOYE, C. BÉRAUD, and R. TOURAINE, Pédiatrie **40:**225, 1951.

A 15-month-old child was admitted to the hospital because of loss of weight, pallor, fever, and a roentgenogram typical for miliary tuberculosis of the lungs. The father and four siblings were hospitalized for pulmonary tuberculosis. The child was treated for one year with 1 gm. of streptomycin daily and *p*-aminosalicylic acid for four months. He recovered clinically, and the roentgenogram showed that multiple small calcified foci remained in the lungs and on the tip of the spleen.

The authors emphasize the rapid clinical response of the child with only slowly progressing calcification according to the roentgenogram. They feel that the tuberculous nature is amply proved by the family history and positive skin test and that the calcifications of the spleen prove the hematogenous spread of the disease.

GLASER, Jerusalem.

MEDIASTINAL ROENTGEN THERAPY IN THE TREATMENT OF PRIMARY TUBERCULOSIS IN INFANTS. M. JEUNE, CL. BÉRAUD, and J. NORMAND, Pédiatrie **40:**937, 1951.

Careful roentgen therapy of the chest, applied after a sufficient interval following the initial febrile episode, can help in shortening the duration of the primary pulmonary tuberculous infection. The influences upon the glands, pulmonary consolidation, and endobronchial lesions are discussed.

GLASER, Jerusalem.

FUNDAMENTAL SURGICAL TREATMENT OF TUBERCULOUS CERVICAL LYMPHADENITIS. E. K. OPPIKOFER, Schweiz. med. Wchnschr. **82:**677 (June 28) 1952.

In the course of three years the author practiced tonsillectomy with or without adenectomy. A short time later the diseased cervical nodes were removed, even when abscesses and fistulas had formed. This was done in 54 patients whose ages varied from 4 to 77 years. Nine of these patients were within the first decade. In these cases the tuberculous nature of the lesions was verified by the pathologist, and the lungs were free from tuberculosis. Primary tuberculous infection of the tonsils is discussed as well as diagnostic features of tuberculous cervical lymphadenitis. It is concluded that the standard treatment of this adenitis is surgical. The results were very good.

AMBERG, Rochester, Minn.

THERAPY OF TUBERCULOUS CERVICAL LYMPHADENITIS WITH SPECIAL CONSIDERATION OF THE VALUE OF TONSILLECTOMY. O. HASLER and A. WEDER, Schewiz. med. Wchnschr. **82:** 682 (June 28) 1952.

The first step in the treatment of tuberculous cervical lymphomas is tonsillectomy. If after this no tendency toward regression is noted, radical extirpation of the lymphoma is desirable. Ten of 59 patients were below 10 years of age.

AMBERG, Rochester, Minn.

CLINICAL AND ROENTGENOLOGICAL EVALUATION OF CHILDREN VACCINATED WITH ANATUBERCULIN (PETRAGNANI-SALVIOLI METHOD) 10 YEARS PREVIOUSLY. A. FERRO and S. TARONNA, Clin. pediat. **33:**771 (Dec.) 1951.

Of 354 newborn infants vaccinated by the Petragnani-Salvioli method 8 to 12 years previously, none had died of tuberculosis, although 75 were known to have had a marked exposure to the disease. Fifty-six per cent of 178 of these children were found on a recent examination to have positive tuberculin tests; by comparison, only 20% of the nonvaccinated children in the community had positive tests.

Some of the children in this group had been exposed to an epidemic of tuberculosis in the Dolo Infant Asylum, where the incidence of primary tuberculosis was 37% in the vaccinated and 53% in the nonvaccinated group.

HIGGINS, Boston.

ON THE PRESENT STATUS OF CHILDREN VACCINATED ORALLY WITH BCG IN BOLOGNA IN THE YEARS 1926-1934. A. DEGLI ESPOSTI and D. GIOVANETTI, Clin. pediat. **33:**781 (Dec.) 1951.

Of 234 infants vaccinated with BCG by mouth 17 to 25 years previously, 7 are known to have died, 3 definitely and a 4th probably from tuberculosis. The authors were able to trace and examine 64 of the 234, who are now about 20 years old. Thirty-one of the 64 showed clinical or roentgenological signs of tuberculosis. Of 12 persons who were vaccinated at about the same time with BCG by the scarification method, 3 showed signs of tuberculosis.

The authors conclude that their data indicate that oral vaccination with BCG is of little or no value and seemingly less effective as a prophylactic procedure than Maragliano's scarification method.

HIGGINS, Boston.

TREATMENT OF CHILDHOOD TUBERCULOSIS WITH AMITHIOZONE (THIOSEMICARBAZONE). E. DEPPERU, Pediatria **59:**821 (Nov.) 1951.

Twenty-eight children with primary tuberculosis were treated with amithiozone (thiosemicarbazone). The initial daily dose was from 5 to 8 mg. daily; this dose was increased daily within the child's tolerance to 25 mg. daily and finally to 2 mg. per kilogram of body weight; the larger doses were given in two divided doses. The medication was effective in overcoming the fever, in lowering the blood sedimentation rate, in improving the child's general condition, and healing the local lesions. In three of the children anemia developed which necessitated the withdrawal of the medication.

HIGGINS, Boston.

MANDIBULAR ACTINOMYCOSIS IN CHILDHOOD. HELMUT WEYERS, Arch. Kinderh. **139:**161, 1950.

This is a description of a case of a 12-year-old girl. A discussion is given of the difficulties in differential diagnosis.

Prior to the patient's admission to the hospital, the mandibular swelling was interpreted as a primary dental infection. Only in a later stage of the disease, when the x-ray findings revealed an irregular bony destruction, was actinomycosis suspected and affirmed by the bacteriological examination. Even large doses of penicillin proved to be ineffective, whereas large doses of sulfonamides arrested the process. Obviously, the combined treatment with x-rays and sulfonamides is most advisable. X-ray treatment favorably influences the actinomycotic process, and the sulfonamides exert an inhibiting effect upon the secondary infections with other pathogenic agents.

GOTTSTEIN, Chicago.

COMPLICATIONS AND "FAILURES" OF BCG IMMUNIZATION. H. SAAME, Ztschr. Kinderh. **68**:276, 1950.

Saame reports 26 cases of patients who were admitted to his institution with the diagnosis or the suspicion of tuberculosis as a result of BCG immunization. Intracutaneous BCG immunization has been practiced on a large scale in Germany for some years. Of these 26 cases in 5 the patients had pulmonary tuberculosis; of these, 3 received immunization in the preallergic phase of spontaneous tuberculosis, one had an ineffective immunization, and in 1 tuberculosis appeared actually nine months after immunization. Four children showed suppuration of the local lymph nodes—probably with secondary infection. In the 17 remaining cases, the suspected diagnosis of tuberculosis was not confirmed on further investigation and observation. The analysis of these 26 cases shows that failure actually occurred in only one child and rather insignificant complications occurred in only four children.

GLASER, Jerusalem.

COLD AGGLUTININS IN THE BLOOD OF CHILDREN WITH TUBERCULOSIS. T. HOCKERTS, Ztschr. Kinderh. **68**:419, 1950.

The author examined the blood of 95 subjects for cold agglutinins. Of these, 70 were children with tuberculosis, 15 were adults with tuberculosis, and 10 were healthy adults. He found increased titers (1:128 or higher) in children with tuberculosis in the secondary stage (hilar nodes with infiltration and miliary tuberculosis with meningitis) but not in healthy adults or in adults with tuberculosis. Intercurrent infections did not influence the cold agglutinations. The author believes that increased copper values in the plasma and changes of the globulin fraction are responsible for the increased cold agglutinins in certain conditions.

GLASER, Jerusalem.

BCG VACCINATION OF SCHOOL CHILDREN. J. J. DALMEIJER, A. VISSER, J. G. WUITE and R. S. ZANDT, Nederl. tijdschr. geneesk. **94**:3226 (Nov. 11) 1950.

BCG vaccination was done on 7,268 pupils of the upper forms of the primary schools of Amsterdam who reacted negatively to 0.1 mg. of tuberculin administered intracutaneously. Eight to 10 weeks later only seven children appeared not to have developed any allergy. Of the total group, 7,010 reacted positively to 0.1 mg. of tuberculin (Mantoux), 79 reacted negatively to 0.1 mg. but positively to 1 mg., and reactions of 172 could not be checked. Use of a good and freshly prepared BCG vaccine and an excellent technique of intracutaneous administration are necessary for the obtaining of good results.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Blood, Heart and Blood Vessels, and Spleen

COARCTATION OF THE AORTA: A STUDY OF SEVENTY CASES IN WHICH SURGICAL EXPLORATION WAS PERFORMED. O. THERON CLAGETT, ROBERT W. JAMPOLIS, A. M. A. Arch. Surg. **63**:337 (Sept.) 1951.

The youngest patient explored was 7 years of age. Forty-nine patients were 20 or more years of age. The authors believe that 15 to 20 years is the optimal age for surgical correction. One-third of the patients were asymptomatic. Easy fatigability, dyspnea, headache, and palpitation were the commonest presenting symptoms. Elevated blood pressure in the upper extremities was invariable. Only three patients had no murmur. Other findings are analyzed and treatment and complications discussed. Of the 70 patients explored, 7 were found to have an inoperable condition and five surgical deaths occurred (all among the first 15 patients operated upon). Long-term follow-up was not attempted.

YANKAUER, Rochester, N. Y.

SPLENOMEGALY IN THROMBOCYTOPENIC PURPURA. LEE EHRLICH and STEVEN O. SCHWARTZ, Am. J. M. Sc. **221**:158 (Feb.) 1951.

One hundred ten cases of thrombocytopenic purpura were studied to determine the incidence of splenomegaly in this disease. Thirteen palpable spleens were found. Twelve of the 13 palpable spleens revealed primary or secondary pathologic changes. Only one instance of a "primary" thrombocytopenia was encountered in which the spleen was palpable.

Secondary splenogenic thrombocytopenic purpura is suggested as the name for the condition in which the thrombocytopenia is secondary to a diseased spleen.

Splenectomy is as effective therapeutically in secondary splenogenic as in primary thrombocytopenic purpura. Leukopenia is found in almost every case of secondary splenogenic thrombocytopenic purpura. The presence of a palpably enlarged spleen in thrombocytopenic purpura practically rules out the "primary" and "allergic" types.

HENSKE, Omaha.

SICKLE-CELL DISEASE: STUDIES ON "IN VIVO" SICKLING AND THE EFFECT OF CERTAIN PHARMACOLOGICAL AGENTS. A. B. HENDERSON, Am. J. M. Sc. **221**:628 (June) 1951.

Twenty-six patients with sickle-cell anemia were observed during the acute and chronic phases of the disease. Increased intravascular hemolysis is a more or less constant feature of the disease, and the resulting anemia and accelerated erythrocytogenesis are found during both periods. Sudden massive destruction of erythrocytes does not appear to explain the symptoms at the time of the crisis.

Variations of in vivo sickling may occur. The clinical crisis may be associated with few or numerous sickled forms in venous blood. Although severe sickling was often associated with the crisis, even severer sickling may be observed without clinical symptoms.

The effects of certain pharmacological agents on the course of the disease are presented, and the results are as follows: 1. An anticoagulant agent, bishydroxycoumarin (Dicumarol), did not prevent a transitory attack of pain. 2. Increase in the blood flow appeared to give transitory relief during a crisis. 3. An oxidation agent (methylene blue) had no effect on the course of the disease. 4. An adequate diet did not appear to affect intravascular hemolysis.

The results of blood transfusions are in agreement with the findings of Kaplan and Lewis.

HENSKE, Omaha.

AORTIC ATRESIA, MITRAL STENOSIS, HYPOPLASIA OF THE LEFT VENTRICLE AND OTHER CARDIAC ANOMALIES IN NEWBORN. JAMES A. GUNN and JOHN B. MIALE, Arch. Path. **50**:464 (Oct.) 1950.

The authors report a case of aortic atresia, hypoplasia of the ascending aorta, mitral stenosis, hypoplasia of the left ventricle, and patent ductus arteriosus and foramen ovale in a newborn boy who died 24 hours after birth. The mother was a primipara with a normal pregnancy. The infant weighed 7 lb. 10 oz. (3,175 gm.) at birth after a rapid but otherwise uneventful labor. This represents the 16th case of the syndrome reported in the literature. The clinical picture of intense cyanosis, weak pulse, low blood pressure, and right axis deviation in the electrocardiogram is typical. The prognosis is very poor, and death usually occurs a few days after birth.

HAW CHAN, San Francisco.

SQUAMOUS EPITHELIAL CYSTS IN THE HEART OF AN INFANT, WITH COINCIDENT CYSTIC CHANGES IN THE OVARIES AND BREASTS. JOSEPH LEIGHTON, JOHN W. HURST, and JOHN D. CRAWFORD, Arch. Path. **50**:632 (Nov.) 1950.

A case in a 10-week-old girl of interventricular septal defect with a saccular deformity of the septal leaf of the tricuspid valve and squamous cysts of the root of the valve leaflet and adjacent septum is reported. The authors consider the cysts as a specific case in the general unanswered problem of the origin of differentiated cells of one germ cell layer in an organ arising from another germ cell layer.

In addition to the cardiac findings, the autopsy study revealed dilated follicular cysts of the ovary (some of which were mature follicles), and prominent dilated duct-structures in the breast tissue. The authors were unable to establish a relationship between these changes and the cardiac anomalies, but they suggest that in cases of cardiac anomalies greater attention should be given to the anatomy of all the endocrine glands to determine whether a recurring, and possibly significant, relation does exist.

HAW CHAN, San Francisco.

SICKLE-CELL DISEASE. HARRY BLOCH, ROBERT J. WALDRON, and GILBERT M. COGAN, J. Pediat. **38**:88 (Jan.) 1951.

The authors agree with previous suggestions that the anemia of sickle-cell anemia is but a symptom of this illness. They report the case of a child with sickle-cell disease whose anemia was corrected. Later a subarachnoid hemorrhage developed, and still later, despite the fact that the child had a hemoglobin concentration of 11 gm., cerebral thrombosis developed. The thrombosis left the child with a residual hemiplegia.

MACDONALD, Pittsburgh.

AURICULAR SEPTAL DEFECTS IN CHILDREN. JOHN D. KEITH and CONSTANCE C. FORSYTH, J. Pediat. **38**:172 (Feb.) 1951.

Auricular septal defect is the sixth commonest congenital heart defect seen in the outpatient clinic at the Hospital for Sick Children, Toronto, Canada. The authors report 14 proved cases with details of diagnostic signs and procedures. One patient, whose defect was closed by Murray, had an associated mitral disease. In this patient the heart size decreased after operation, but the authors do not believe that she is otherwise noticeably improved. They indicate that the operation may be of more benefit for patients with no mitral complications.

MACDONALD, Pittsburgh.

CONGENITAL VALVULAR PULMONARY STENOSIS WITH OR WITHOUT AN INTERATRIAL COMMUNICATION: PHYSIOLOGIC STUDIES AS DIAGNOSTIC AIDS. FORREST R. ADAMS, L. GEORGE VEASY, and JOSEPH JORGENS, J. Pediat. **38**:431 (April) 1951.

Valvular pulmonary stenosis as an isolated lesion and pulmonary stenosis associated with interatrial communication have been considered to be relatively rare congenital abnormalities. Physiological studies of over 200 patients with congenital heart disease made by the authors revealed 19 with isolated valvular pulmonary stenosis accompanied by an intra-atrial communication. An additional patient had pulmonary stenosis with patent ductus arteriosus. The investigation included right heart catheterization and oximetry studies. The authors note that pulmonary stenosis should be suspected in patients with severe dyspnea, in whom the pulmonic second sound is absent or decreased in intensity and roentgen study shows a large pulmonary artery out of proportion to the vascular lung markings. Confirmation of the diagnosis may be made by cardiac catheterization and oximetry.

MACDONALD, Pittsburgh.

ACUTE THROMBOSIS OF THE FEMORAL ARTERY IN AN INFANT. SAMUEL FELDMAN, JOSEPH GOODGOLD, and HAROLD LEVY, J. Pediat. **38**:498 (April) 1951.

Thrombosis of the femoral artery followed puncture of the femoral vein for diagnostic blood studies in a 1-year-old infant. Treatment included sedation (Meperidine), anticoagulants, heparin sodium (Depo-Heparin), wrapping (sterile gauze and absorbent cotton), antibiotics (penicillin), repeated lumbar paravertebral ganglion blocks from the first through the fourth lumbar segment (with 1% procaine hydrochloride), and elevation of the head. A focal slough and desquamation of the skin of the affected leg developed, but the infant recovered.

MACDONALD, Pittsburgh.

INFECTIOUS MONONUCLEOSIS IN THE NEGRO. JOHN F. HARLEY, J. Pediat. **39**:303 (Sept.) 1951.

Because of an associated membranous tonsilitis, infectious mononucleosis may be mistaken for diphtheria. Cultures and clinical and hematologic signs, with heterophile agglutination titers, will establish the proper diagnosis. It has been implied that the disease is rare in the Negro. Harley, of Louisville, says that it is as common in the Negro as in the White.

MACDONALD, Pittsburgh.

PERIARTERITIS NODOSA IN INFANCY. LESTER ADELSON, J. Pediat. **39**:346 (Sept.) 1951.

This is a case of periarteritis nodosa in a 4½-month-old infant, rare in itself. Adelson blames penicillin as the probable cause.

MACDONALD, Pittsburgh.

TREATMENT OF LEUCEMIA IN CHILDHOOD. KENNETH C. MICKLE, GEORGE V. MUSCATO, and ALICE LEMANSKI, J. Pediat. **39**:442 (Oct.) 1951.

Despite its toxicity 4-aminopteroylglutamic acid (Aminopterin) is the drug of choice in the treatment of acute leukemia.

MACDONALD, Pittsburgh.

STUDIES IN SICKLE-CELL ANEMIA: II. CLINICAL MANIFESTATIONS OF SICKLE-CELL ANEMIA IN CHILDREN. ROLAND B. SCOTT, L. OTTO BANKS, MELVIN E. JENKINS, and ROBERT P. CRAWFORD, J. Pediat. **39**:460 (Oct.) 1951.

The authors report a series of 37 cases of sickle-cell anemia. Of the patients, 27 were male. The commonest symptoms were anorexia and abdominal and joint pains.

The authors recommend the parameter test of Winsor and Burch as an aid in differential diagnosis.

Corticotropin (ACTH) and cortisone are valuable in the control of the symptoms of hemolytic crises.

MACDONALD, Pittsburgh.

PRESENCE OF MYELOKENTRIC AND LYMPHOKENTRIC ACID IN SERA OF PATIENTS WITH LYMPHOMATOID DISEASES. CHARLES G. FOSTER and F. R. MILLER, Proc. Soc. Exper. Biol. & Med. **75**:633 (Dec.) 1950.

Inasmuch as the urine of patients with leukemia and other lymphomatoid diseases has been shown to contain myelokentric and lymphokentric acid, which seem to play a part in proliferation and possibly the maturation of myeloid and lymphoid cells, the authors undertook studies of a serum for such substances. From 20 to 40 cc. of blood was removed from each patient, and the serum was drawn off and introduced into the peritoneal cavity of a guinea pig. Samples of serum were obtained from 9 patients with chronic myeloid leukemia, 6 with chronic lymphoid leukemia, 6 patients with monocytic leukemia, 4 with Hodgkin's disease, and 12 normal persons. Fifty-nine animals were inoculated with serum from the diseased patients and 35 from the normal subjects. Lymph nodes were carefully studied in all animals—some at 8 hours, some 24, and some 48 hours after injection of the serum. It was found that lymph nodes from animals which received serum from patients with chronic myeloid leukemia have a tendency toward a loss of lymphoid structure, somewhat similar to that found following the use of cortisone or corticotropin (ACTH). There was, however, an increase in fibrosis and underlying connective tissue. The nodes from the two groups that received sera from patients with chronic lymphoid leukemia all showed a tendency toward increased lymphoid production. In both groups there was definite increase in eosinophiles. The increased lymphopoiesis in the lymph nodes of animals which received serum from patients with chronic lymphoid leukemia is similar to that in animals that have received lymphokentric acid in urinary extracts.

HANSEN, Galveston, Texas.

CITROVORUM FACTOR AND FOLIC ACID IN TREATMENT OF MEGALOBLASTIC ANEMIA IN INFANCY. CALVIN W. WOODRUFF, J. CYRIL PETERSON, and WILLIAM J. DARBY, Proc. Soc. Exper. Biol. & Med. **77**:16 (May) 1951.

Citrovorum factor, a nutrient required by Leuconostoc citrovorum, is a metabolite of folic acid and is excreted in increased amounts in the urine of man and rats after administration of folic acid. Its metabolic activity in man is indicated by its ability to reverse the toxic effects of 4-aminopteroylglutamic acid (Aminopterin) and to induce a hemopoietic response in patients with pernicious anemia. The authors report on two infants, white fraternal twins, aged 10 months, who suffered from megaloblastic anemia. In one infant, 72 hours after the first injection intramuscularly of 500,000 units of citrovorum factor, there was an increase in the number of normoblasts in the marrow. In the second infant, on the fourth day after the same amount of citrovorum factor, a marrow specimen revealed active hemopoiesis with normoblasts predominating. The amounts given were equivalent to 75 γ of the anhydrous free acid. Folic acid

was effective in two cases of this syndrome in which the oral dose levels were 500 γ and 200 γ daily. The authors state that the pathogenesis of megaloblastic anemia is not established, nor has the dietary need for folic acid for healthy infants been demonstrated.

HANSEN, Galveston, Texas.

SULFHYDRYL CONTENT OF NORMAL HEMOGLOBIN AND HEMOGLOBIN IN SICKLE CELL ANEMIA. SIDNEY H. INGBAR and EDWARD H. KASS, Proc. Soc. Exper. Biol. & Med. **77**:74 (May) 1951.

The authors sought to determine whether the reduced SH-content of sickle cell hemoglobin differs from that of normal hemoglobin. Studies were made of four normal persons, five patients with sickle cell anemia, and two with sickle cell trait. The hemoglobin solution was prepared by collecting venous blood in Alsever's solution. The cells were washed with saline and hemolyzed with distilled water. Sodium chloride, 2.0%, was added, and the solution was allowed to stand overnight in the refrigerator and the stromal precipitate was removed by centrifugation at 4 C. and 16,000 rpm for one and one-half to two hours. The hemoglobin solutions were dialyzed until they were entirely free of non-protein-producing substances. The titratable SH-content of hemoglobin was determined amperometrically in saline and found to approximate normal hemoglobin (2.0 SH groups per molecule), whereas for patients with sickle cell anemia the mean value was 3.0 SH groups per mole of hemoglobin. In two patients with sickle cell trait, the SH content was greater than that of normal hemoglobin and less than that of sickle cell anemia hemoglobin.

HANSEN, Galveston, Texas.

EFFECT OF PLASMA INFUSIONS IN ACUTE LEUKEMIA IN CHILDREN. J. DARTE, C. E. SNELLING, and W. L. DONOHUE, Canad. M. A. J. **66**:576 (June) 1952.

Treatment of two children with continuous plasma infusion produced no hematological response. Although the plasma was less than 48 hours old, it apparently did not contain a measurable amount of either an antileukemic or a leucocyte-maturation factor.

McGUIGAN, Evanston, Ill.

LYMPHOSARCOMA OBSTRUCTING THE SMALL BOWEL. Y. WUIDART, Presse méd. **59**:467 (April 7) 1951.

Rarely does lymphosarcoma begin in the small intestine, and even more rarely does it produce primary occluding obstruction. In the case presented, a boy of 8 years was hospitalized because of classic signs and symptoms of obstruction. At operation, a large tumor was discovered and removed. Histological examination revealed the typical picture of lymphosarcoma.

DAFFINEE, Melrose, Mass.

EFFECT OF THE HYPOPHYSEAL HORMONES ON HEMATOPOIESIS. G. CARDINI and M. VERROTTI, Clin. pediat. **33**:219 (April) 1951.

Four studies were made, each with 10 children 10 to 24 months of age. Intramuscular injections were given for 10 days with one of the following pituitary gland products: whole posterior pituitary gland extract, whole anterior pituitary gland extract, and chorionic gonadotropin. Blood and bone marrow smears were taken on the 1st, 10th, and 30th days after the last injection.

The posterior lobe extract led to a definite hyperplasia of the blood cells of the erythropoietic series. It would appear that there is a red blood cell-stimulating substance in the posterior pituitary lobe.

The anterior pituitary lobe extract led to a definite increase in the number of blood cells of the granuloblastic series and a parallel decrease in those of the lymphocytic series; there was also a slight increase in red blood cell formation.

Chorionic gonadotropin were without any effect on hemopoiesis.

HIGGINS, Boston.

VENTRICULAR PAROXYSMAL TACHYCARDIA IN AN INFANT. L. PARENZAN and G. GRANATA, Minerva pediat. **3**:544 (Oct.) 1951.

An infant had many attacks of ventricular paroxysmal tachycardia, beginning at the age of 11 months, gradually decreasing in frequency, and stopping completely six months later. An electrocardiographic record is reproduced showing the transition point between the tachycardia and normal rhythm.

HIGGINS, Boston.

CAPILLARY FRAGILITY TESTS ON CHILDREN IN A SUMMER HEALTH CAMP. C. BOGGERO, Minerva pediat. **3**:557 (Oct.) 1951.

Tests made at a health camp near Genoa revealed that a new instrument, the Angelino Petechiometer, which applied suction over an area of skin, was very helpful in evaluating the degree of capillary fragility. A formula containing vitamins C and E and rutin is recommended for reducing capillary fragility.

HIGGINS, Boston.

NIEMANN-PICK DISEASE. GESUALDO CROCCO, Pediatria **49**:710, 1951.

The author describes a case of Niemann-Pick disease which is particularly interesting because of marked megaloblastic metaplasia of the bone marrow. The pathogenesis of the megaloblastosis is discussed.

FROM THE AUTHOR'S SUMMARY.

PERIARTERITIS NODOSA IN A CHILD. RENATO FIANDACA, Riv. clin. pediat. **49**:791 (Nov.) 1951.

The author describes the clinical symptomatology, the pathological anatomy, and the etiopathogenesis of nodosa periarteritis and briefly surveys the therapies tried to date. He reports a chronic case of the disease in a child aged 8.

FROM THE AUTHOR'S SUMMARY.

THERAPEUTIC EFFECTS OF VITAMIN E IN FOURTEEN CASES OF HEMOPHILIA. PAOLO PROSPERI and ALFREDO LOTTINI, Riv. clin. pediat. **49**:808 (Nov.) 1951.

The authors report on the results of vitamin E treatment (in large doses) of 14 patients affected by hemophilia, 12 of whom were affected by real hemophilia and 2 by acquired pseudohemophilia.

The most brilliant results were obtained in the reduction of the coagulation time; in nearly all cases, this fell, during treatment, to near normal, normal, and subnormal values.

Occasional suspensions of treatment led to a new prolongation of the coagulation time. The therapy proved to have a benign influence on the course of recent hemophilic arthropathies by acting rapidly in prevention of the formation of extensive hemarthrosis, quickly reabsorbing small articular hemorrhages, and during the course of treatment checking the formation of hemorrhages in general.

Many of the subjects treated were enabled after months of inactivity to resume their normal life; some, even after traumatic lesions (serious bruises, extraction of teeth, etc.), did not suffer any hemorrhagic consequences. In all cases a remarkable improvement of general condition was evident, with appearance of secondary sexual characters and hormonal maturation in patients who have reached the age of adolescence but have not yet reached puberty, and with increase of fatty tissues and improvement of cenesthesia in adults.

Possible though rare relapses were promptly resolved by a timely increase of the vitamin E dose.

The authors formulate some hypotheses on the interference of vitamin E with the delicate mechanism of blood coagulation and specifically with hemophilia. They suggest that the effects are vascular, plasmatic, and hormonal.

FROM THE AUTHORS' SUMMARY.

TRUE PERSISTENT TRUNCUS ARTERIOSUS. R. KREUTZER, J. A. CAPRILE, F. WESSELS, and G. C. FERRI, Arch. argent. pediat. **36**:25 (July) 1951.

The authors review the diagnostic criteria and present clinical and anatomical observations on two patients, aged 5 and 2 months, respectively.

PANOS, Galveston, Texas.

CONGENITAL CARDIOPATHIES AMENABLE TO SURGICAL TREATMENT. J. M. DURAN ANDREU, Arch. pediat. **2**:199 (Sept.) 1950.

The possibility of surgery to relieve such structural defects as patent ductus arteriosus, stenosis of the pulmonary artery, and coarctation of the aorta has made the diagnosis of congenital heart disease much more important.

The author discusses the anatomy of the fetal circulation as compared with postnatal circulation. The symptoms, findings by x-ray, electrocardiogram, angiocardiography, and catheterization are described for each type of operable defect. The author also discusses the tetralogy of Fallot, the details of the operation procedure, and the necessity of distinguishing between the tetralogy of Fallot and Eisenmenger's complex.

The brief case histories of two infants are included, one with patent ductus arteriosus and the other with tetralogy of Fallot.

ALLEN, San Francisco.

DIAGNOSIS AND THERAPY OF CONGENITAL ANGIOCARDIOPATHIES. J. JACOBI, M. LOEWENECK, and F. NORTHOFF, Deutsche med. Wchnschr. **77**:193 (Feb. 15) 1952.

On the basis of 110 patients with congenital heart disease, general and special methods of examination are discussed, including catheterization of the heart, intracardial pressure and blood oxygen determinations, and angiocardiography. Symptomatology and classification are also discussed. Operative procedures with their dangers and complications are presented.

AMBERG, Rochester, Minn.

EFFECT OF ADRENOCORTICOTROPIC HORMONE (ACTH) ON CIRCULATING EOSINOPHILES IN INFANTS. C. G. BERGSTRAND, B. EHLLSTRUM and B. JONSSON, Acta pædiat. **41**:393 (Sept.) 1952.

The spontaneous change in the number of circulating eosinophiles from 8 a. m. to 12 m. was investigated in full-term and premature infants 0 to 7 days old and in full-term infants 30 to 120 days old. This change is sometimes considerable. The change in the number of eosinophiles from 8 a. m to 12 m. after the injection of small doses of corticotropin (ACTH) (0.33 to 0.67 mg. per kilogram of body weight) was investigated in the same groups of children. When the mean values of the change, expressed in percentage of the number of eosinophiles at 8 a. m., are considered, a decrease after administration of corticotropin is found in all groups. A statistical analysis shows that no significant difference in the degree of this decrease exists between premature and full-term newborn infants (0 to 7 days old), nor is it possible to find such a difference between full-term infants 0 to 7 days old and infants 30 to 120 days old.

The degree of response in the premature could not be correlated with weight or age of the infant. Cortisone had no significant effect on the number of eosinophiles when tested in the same way as was corticotropin.

It is pointed out that, if it is assumed that the eosinophile response to corticotropin is a test of adrenocortical function, the data collected in his investigation are difficult to coordinate with the hypothesis that there exists in the newborn a physiological transitory adrenal insufficiency.

FROM THE AUTHORS' SUMMARY.

GROWTH AND ACTION OF THE HEART IN UTERO. R. H. HOEKSTRA, Maandschr. kindergeneesk. **19**:493 (Jan.) 1952.

The physiological and the pathogenic movements which take place during growth before and after birth seem to be analogous. The prenatal movements of growth and those accomplished by the heart and by the great vessels during respiration occur around a similar system of axes, which is erected in a physiological position.

The abnormal positions of the heart which have been observed at autopsy or by thoracotomy agree with the end-positions of a movable model of the heart, which has been constructed so as to be able to turn around an axis which is placed in a similar position.

The human heart when in abnormal position must have undertaken similar movements, called inversion or dextroversion.

Pathogenic growth seems to move round axes erected in calculable and pathogenic positions. For instance, the pathogenic growth of the aorta seems to move round an axis placed in a left

and dorsal position. This pathogenic reversion of the aorta gives rise to the formation of primary and mechanical defects of the circulatory system.

The kinds of pathogenic growth which appear after the formation of the primary and mechanical defect give rise to the formation of secondary dynamic heart defects. As to the right and ventral position of the axis of the aorta, reversion puts an end to this pathogenic development. This curative reversion of the aorta is therefore the cause of spontaneous recovery of the primary defect. Frequently, however, the secondary dynamic defects remain after the primary mechanical defect has disappeared.

The interpretation of the physiological and the pathogenic growth of the heart and its main arteries as here described permit an exact diagnosis of many complicated malformations of the circulatory system after mere examination of a straight x-ray picture of the chest. Moreover, this working hypothesis gives remarkable results in connection with the knowledge of the pathogenesis of congenital heart diseases, as well as with the knowledge of the origin of the malformations of the great vessels, the trachea, the bronchi, the lungs, and the esophagus.

FROM THE AUTHOR'S SUMMARY.

Diseases of Nose, Throat, and Ear

FOREIGN BODIES, EXOGENOUS AND ENDOGENOUS, IN THE RESPIRATORY TRACT. R. ROMAS and R. PACH VINALS, Arch. pediat. **11**:557 (March-April) 1952.

Eleven cases with x-rays and complete clinical histories of foreign bodies in various parts of the respiratory tract are presented. Some cases were emergencies and needed immediate attention, while others, because of their location, had been incorrectly diagnosed. A lung abscess developed in a child following aspiration of a small portion of a peanut which lodged in a small bronchiole. The child had been treated at intervals for various upper respiratory infections for a total of 15 months, and only when the vomiting and odor suggested an abscess a true diagnosis was made.

Another patient had been treated for pertussis and bronchopneumonia, but the true cause was not determined for a year. Various other cases in which foreign bodies of vegetable origin were involved—peanuts, beans, etc.—and metallic objects, such as coins and buttons, are reported. Endogenous foreign bodies due to laryngotracheobronchitis, necrotic tracheobronchitis, endotracheal abscesses, diphtheria, tuberclulosis of tracheobronchial lymph nodes, and neoplasms are also discussed. Atelectasis may result from any one of these diseases, and in the case of a 5-year-old girl with a rupture of tuberculous cavity into the bronchus this occurred. The caseous material acted as a foreign body. Besides the surgical or bronchoscopic intervention, antibiotics are always indicated. In the case of the child with tuberculosis, streptomycin was given before bronchoscopy.

ALLEN, San Francisco.

A CONSIDERATION OF THIAMINE SUPPLEMENT IN PREVENTION OF STUTTERING IN PRESCHOOL CHILDREN. LESTER L. HALE, J. Speech & Hearing Disorders **16**:327 (Dec.) 1951.

Thiamine hydrochloride, 10 mg. three times daily, was administered to stutterers of preschool age and a placebo to a control group of preschool stutterers. After one month treatment was reversed, and observation was continued another month. Neither the clinicians nor the parents knew which treatment the child was receiving. Observable speech improvement occurred in 55% of all thiamine-treated patients. Improvement occurred primarily in the first two weeks of treatment. Eighty per cent of the 2 and 3 year old children and 50% of the 4 year old children showed improvement. The author feels that thiamine may be helpful in the prevention of stuttering in preschool children.

PALMER, Wichita, Kan.

SYNDROME OF RESPIRATORY OBSTRUCTION OF LARYNGOTRACHEAL ORIGIN. BERNARDO BAMBACH and ROS VOLOSKY, Revista chilena pediat. **23**:336 (Aug.) 1952.

The greatest frequency of the nondiphtheritic respiratory obstruction syndrome is found in children of less than 2 years, and diphtheritic obstruction in children older than 2 years. The greatest number of cases of both types are found in spring. The frequency of nondiphtheritic

obstructive respiratory syndrome has increased in the last 10 years; not so the mortality, which, in comparison with that shown in foreign reports, is low in Chile. The most frequent preceding condition in nondiphtheritic respiratory obstructions is grippe, measles following it in frequency.

The use of diphtheria antitoxin therapy in cases in which diphtheria is not involved is rather high, owing to badly organized collaboration with the ear, nose, and throat service. The authors consider that diphtheria antitoxin should be used in one single and adequate dose. Accidents in tracheotomy are relatively low in the authors' hospital.

FROM THE AUTHORS' SUMMARY.

MASTOIDITIS IN THE INFANT: CONCEPT AND DIAGNOSIS. R. RAMOS and R. POCH VINALS, Arch. pediat. **2**:219 (Sept.) 1950.

Acute mastoiditis is still far too common in Spain. The authors believe the reason to be that the diagnosis is sometimes difficult for the general practitioner to make. They describe the anatomy of the mastoid antrum in the infant and the ease with which it may become involved during an otitis media infection in infants. This may occur without much evidence of drainage from the ears.

The diagnostic signs, both clinical and by roentgenology, are discussed, with a number of illustrations. General symptoms and those referable solely to ears are discussed, as well as the types of illnesses in which mastoiditis may be a concomitant or sequel; however, the author says it must always be remembered that it is an infection and not just as illness which coexists with the nutritional and diarrheal diseases of infancy.

The techniques of transillumination and the procedure for the drainage of the mastoid are given. If antibiotics do not give immediate relief, one should use x-rays and possibly operate for drainage.

Mastoiditis due to tuberculosis is nearly always fatal because it is usually found along with generalized tuberculosis or with meningitis, and unless diagnosed very early it is very unlikely to be amenable to treatment.

MARY ALLEN, San Francisco.

Diseases of Lungs, Pleura, and Mediastinum

PROGNOSIS OF PNEUMONIA IN INFANCY AND CHILDHOOD. A. HOLZEL and B. WOLMAN, Arch. Dis. Childhood **25**:282 (Sept.) 1950.

Two hundred fourteen cases of pneumonia in infancy and childhood treated during the years of 1946, 1947, and 1948 in two Manchester children's hospitals are reviewed. The results of treatment with sulfonamides, penicillin, and combinations of sulfonamides and penicillin are compared.

The highest mortality occurred in infants under 6 months of age, and combined therapy did not seem to affect the prognosis in this age group. There was a steep fall in the mortality rate for infants more than 6 months but under 1 year of age, and a very low death rate for older children.

Attempts to lower the general mortality from pneumonia must be directed toward treatment during the first six months of life.

Twenty patients died within 24 hours of admission to the hospital. Reasons for the delay in diagnosis are discussed.

Leucocyte counts for 80 infants under 2 years of age are given. No prognostic significance can be attributed to the total white cell count or to the percentage of polymorphonuclears.

KELLY, Milwaukee.

CLINICAL AND ROENTGENOLOGICAL STUDY OF MEDIASTINAL PLEURITIS IN CHILDREN. P. MENGHI and L. PARENZAN, Minerva pediat. **3**:571 (Nov. 1) 1951.

Fifteen children, 1½ months to 10 years of age, received diagnoses of mediastinal pleurisy by reason of roentgenological and clinical findings. Eight of the children had positive tuberculin reactions. Dyspnea, a dry cough, and shallow respiration with suppression of the breath sounds were frequent symptoms of the condition. Pain in the chest was present in only two patients, one of whom had pneumococcal empyema. The pleurisy disappeared in each case within a few months following antibiotic and symptomatic treatment.

HIGGINS, Boston.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

INCLUSION DISEASE OR GENERALIZED SALIVARY GLAND VIRUS INFECTION. MARGARET G. SMITH and FRANK VELLIOS, Arch. Path. **50**:862 (Dec.) 1950.

The authors present 20 cases of inclusion disease of infants and children. They believe that the intracellular inclusions found in epithelial and sometimes mesenchymal cells have a distinct morphology and are pathognomonic of the disease, that there is reasonable evidence that human inclusion disease is caused by a virus, and that the virus concerned is the salivary gland virus. Some of the conclusions that the authors made on the basis of their observations are as follows:

Generalized salivary gland virus infections occur, in the majority of instances, during the first two years of life. The infection may occur in utero without the mother's showing any evidence of illness. Death due to the intrauterine infection may occur in utero or in the neonatal period. In infants under 2 months of age generalized salivary gland virus infection is usually a primary fatal disease and its most frequent clinical and anatomical manifestations are those of a blood dyscrasia or of hepatic damage. However, the character of the disease may vary, since the viral infection may involve with variable intensity many organs of the body. In children over 2 months of age inclusion disease is associated with diverse clinical histories and anatomic changes. It may be the primary disease or, more frequently, secondary to some other disease. There is suggestive evidence that disturbances of cellular metabolism (e. g., those of vitamin deficiencies) may predispose to generalized salivary gland virus infections. Remaining unexplained is the association of pertussis and generalized salivary gland virus infection in a third of the cases reported in the literature.

HAW CHAN, San Francisco.

MECKEL'S DIVERTICULUM: A SURVEY OF ONE HUNDRED AND THREE CASES. G. D. JAY III, R. R. MARGULIS, A. B. MCGRAW, and R. R. NORTHRIP, Arch. Surg. **61**:159 (July) 1950.

One hundred three cases of Meckel's diverticulum were analyzed. The incidence in the general population is between 1 and 2 %. Acute disease processes in Meckel's diverticulum are most likely to occur in the younger age group. In children, the salient features are rectal bleeding, with low blood hemoglobin levels, pain or tenderness in the right lower quadrant and the periumbilical area, nausea, and vomiting. Seventy-two per cent of the diverticula lie within the terminal 36 in. (0.9 meter) of ileum. However, 28% of the lesions will be missed if search of the ileum is not made above this level.

In the cases in which Meckel's diverticulum which produced symptoms, 60% of the specimens examined contained a gastric type of mucosa. In the group in which the diverticulum was incidentally found at operation or autopsy only 22 and 17%, respectively, contained such mucosa.

KAISER, Rochester, N. Y.

CLINICAL FEATURES OF ACUTE GASTROENTERITIS, PRESUMABLY VIRAL IN ETIOLOGY. S. GEORGE WOLFE and CLARENCE H. WEBB, New Orleans M. & S. J. **104**:273 (Jan.) 1952.

An epidemic of gastroenteritis characterized by explosive onset with vomiting, followed by high fever and diarrhea, has been widely prevalent during the winter season. Laboratory findings in 200 cases showed a tendency to normal or low leucocyte counts, presence of abnormal lymphocytes in 40% of the cases, and negative bacteriologic results from stool cultures. The disease appears to be of viral origin; throat garglings and stools reproduced the disease in 53% of volunteer subjects. The virus is predominantly enterotropic, although there were evidences of nervous, respiratory, and hepatic involvement.

MCGUIGAN, Evanston, Ill.

DISCUSSION ON THE TREATMENT OF CONGENITAL HYPERTROPHIC PYLORIC STENOSIS. KENNETH H. TALLERMAN and DENIS BROWN, Proc. Roy. Soc. Med. **44**:1055 (Dec.) 1951.

Reversing a previous trend, which until 1944 had regarded the treatment of infantile congenital hypertrophic pyloric stenosis as essentially surgical, the author in 1945 began regarding such conditions as medical conditions until proved otherwise.

The basis of medical treatment was the use of atropine methyl nitrate, stomach washing with saline solution twice daily, subcutaneous saline solution for dehydration, and adequate caloric intake. Sixty-seven patients were treated, 41 by medical means alone with one death (2.5% mortality); 26 cases came to surgery, with five deaths (19% mortality). The mortality figures of this surgically treated group were somewhat higher than those of a number of other series of operations, which averaged about 14% mortality.

As approximately two-thirds of all patients responded satisfactorily to medical treatment alone, the author believes it is wise to give an infant the benefit of medical treatment in the first instance, provided surgical aid is sought if he fails to respond to medical treatment alone. One-fiftieth grain (1.2 mg.) of atropine methyl nitrate is the minimum daily dose which should be prescribed. Two or three days of medical treatment will almost always determine whether or not surgical treatment is necessary. Medical treatment is always necessary, and surgical intervention may subsequently be required. The technique of Ramstedt's operation with local anesthesia is described.

HEARD, Monterey, Calif.

ETIOLOGY AND TREATMENT OF ENTERITIS IN CHILDREN. A. SCHIAVINI, Lattante **22**:356 (June) 1951.

Atypical types of Escherichia coli, mostly Esch. Neopolitani, were recovered from the stools of 47 out of 75 infants with diarrhea. Eight out of 100 infants had Salmonella typhimurium in their stools. Various antibiotic preparations were used in the treatment of these patients in Charity Hospital in Novara.

HIGGINS, Boston.

ACTION OF DYSENTERY TOXIN AND OF THE COLON BACILLUS ON THE ENZYMATIC ACTIVITY OF THE DUODENAL MUCOSA. F. MULÈ, I. GARUFI, and F. BARCAROLI, Pediatria **59**:320 (May) 1951.

Minced duodenal mucosa from infants who had died a short while before was used for testing the effect of dysentery toxin and of Escherichia coli on enzymatic activity. This activity was determined by a micromethod for measuring oxygen consumption. The dysentery toxin and the Esch. coli increased the oxygen consumption by the mucosa, but tyramine alone did not do so.

HIGGINS, Boston.

INTESTINAL INVAGINATION IN CHILDHOOD: ANALYSIS OF FIFTY-FIVE CASES. W. GALLUCI and A. GIANELLI, Pediatria **59**:644, 1951.

The authors analyze 55 cases of intussusception in infants. They give the clinical features of the disease and discuss especially the importance of the neurovegetative factor from the pathogenetic point of view, the value of a classification of the mechanism of onset, the importance of the pain associated with the other peculiar symptoms, the importance of x-ray findings, the indications for treatment with barium enema and the limits of this treatment, the operative technique, and the prognosis.

In conclusion the authors discuss intussusception in children and describe the peculiar features of this form.

FROM THE AUTHORS' SUMMARY.

NEW METHOD OF TREATMENT OF HABITUAL VOMITING. R. RAMOS and M. CONILL SANTIAS, Arch. pediat. **2**:189 (Sept.) 1950.

The details of treatment of infants with chronic vomiting with carob flour are described. The history of its use is given, the physical and chemical properties are described, and the details for its use with fresh milk and other commercial milk preparations are given in detail.

Of 17 patients affected by gastric atony of various origins, 10 showed immediate and marked improvement, 6 showed varying degrees of improvement, and 1 was unimproved.

Gastric peristalsis was improved, and the physical properties of carob flour, such as density, viscosity, and elevated colloidal protective power, seemed to diminish excitability in children with spastic stomachs. There was in all cases less gas, and this lessened the distention commonly associated with these cases.

Carob flour contains protein, mannose, and galactose, but does not contain starch.

Occasionally there would be a recurrence of the vomiting, with presence of a new infection or other illness. In these cases antibiotics were given, but in no case were drugs given to reduce muscle spasm.

ALLEN, San Francisco.

ANOMALIES OF ROTATION OF THE INTESTINE. JOSE RIVAROLA and MARCOS TURNER, Arch. argent. pediat. **4**:227 (Oct.) 1951.

A diagnostic suspicion and a roentgenological examination of the digestive tract prompted the treatment of a 3½-year-old child who almost from birth suffered episodes of intermittent, intractable, and bilious vomiting. Rotation and fixation of the middle intestinal loop caused episodes of incomplete occlusion with formation of a megaduodenum and finally a more serious volvulus with a picture of severe duodenal occlusion and humoral changes. Intervention restored the intestinal flow and put an end to these troubles, which, because of their frequency, had caused general retardation of development. The authors stress the importance of suspecting this congenital disturbance in every child who has repeated vomiting and of confirming it by roentgenological study.

A revision of the national bibliography on this subject and an explanation of the etiology and clinical and roentgenological picture of these disturbances are included.

FROM THE AUTHOR'S SUMMARY.

CONGENITAL ATRESIA OF ESOPHAGUS. JULIO C. BARANI, Arch. pediat. Uruguay **22**:776 (Oct.) 1951.

The symptoms and the roentgenographic confirmation of congenital atresia of the esophagus are explained. A case is cited of a girl who, when she was 4 days old, was operated upon for congenital atresia of the esophagus; this is the first case in Latin America in which the operation was successful.

FROM THE AUTHOR'S SUMMARY.

HEPATITIS AND PREGNANCY. G. A. v. HARNACK and G. A. MARTINI, Deutsche med. Wchnschr. **77**:40 (Jan. 11) 1952.

In the offspring of mothers who have had virus hepatitis early in pregnancy an inner-ear hearing difficulty was observed and a anencephalus. However, taking into consideration the authors' own studies on 26 cases and those of Selander on 25 cases, it would appear that the general ratio of deficiencies is not surpassed.

AMBERG, Rochester, Minn.

CONTRIBUTION TO THE ILEUS STATES IN HIRSCHSPRUNG'S DISEASE. L. ZEMAN, R. TRAVNICEK, and K. GROSS, Pediat. listy **5**:308 1951.

The authors describe a case of megacolon congenitum in a newborn infant. The clinical picture was complicated by a relapsing obstruction of the intestinal passage right from the first days. As one cause of the ileus a lateral invagination of the large intestine was found; in the terminal phase volvulus was found; shortly after operation for the volvulus the child died, at the age of 2½ months.

The anatomical, pathological, and histological findings are given. The authors have attempted to explain the invagination and fit it into the clinical picture of megacolon congenitum. They have summarized the hitherto prevailing views on the pathogenesis of Hirschsprung's disease.

FROM THE AUTHORS' SUMMARY.

Nervous Diseases

HERPES SIMPLEX ENCEPHALITIS. DAVID R. GINDER and C. MERRILL WHORTON, J. Pediat. **39**:298 (Sept.) 1951.

Ginder and Whorton report a fatal case of herpes simplex encephalitis in a 22-month-old infant. This is the fifth fatal case reported in the literature.

MACDONALD, Pittsburgh.

TREATMENT OF CONVULSIVE DISORDERS. Z. R. MILLER, Minnesota Med. **35**:1025 (Nov.) 1952.

A brief review of epilepsy and a classification of the types of seizures are presented.

Anticonvulsive therapy is divided into general, psychological, drug, dietary, and surgical treatment. For control of motor seizures the hydantoins and barbiturates alone or in combination are the best. For the petit mal seizures, the diones are most specific. The dosage of drugs is an individual problem.

The bromides diphenylhydantoin (Dilantin) sodium, mephobarbital (Mebaral), and phenobarbital are relatively safe drugs. Methylphenylethylhydantoin (Mesantoin), phenacemide (Phenurone), trimethadione (Tridione), and paramethadione (Paradione) cause side-reactions and in 1 or 2% of cases may elicit dangerous toxic reactions. Phenacemide is known to produce liver damage. The author stresses the need for regular check-ups and periodic hematologic studies in this group of patients.

STOESSER, Minneapolis.

CEREBRAL ANOXIA IN INFANTILE DEHYDRATION. E. KERPEL-FRONIUS, F. VARGA, and K. KUN, Arch. Dis. Childhood **25**:158 (June) 1950.

The oxygen saturation of the blood of the longitudinal sinus was determined in 11 dehydrated infants. The decrease in oxygen saturation was parallel to the gravity of the clinical condition. A close correlation was found between the decrease of the oxygen saturation of the cerebral venous blood and anhydremic shock as measured by circulation time. The longer the circulation time, the lower was the oxygen saturation of the cerebral venous blood. The cerebral symptoms characteristic of a toxic condition in dehydration appeared when the oxygen saturation of the cerebral venous blood approached 25%. Deep coma was observed when the latter decreased to less than 15%. Thus, the cerebral symptoms of severe dehydration appear to be due to cerebral anoxia of the stagnating type.

KELLY, Milwaukee.

SYNDROME RESEMBLING PROGERIA: A REVIEW OF TWO CASES. CATHERINE A. O'NEILL and MARY M. DINGWALL, Arch. Dis. Childhood **25**:220 (Sept.) 1950.

Two microcephalic dwarf brothers are described, with details of the physical and psychological investigations. Reasons are advanced for suggesting that these are cases of multiple germ plasm defect, probably due to a recessive gene, and that this condition is allied to progeria.

KELLY, Milwaukee.

SURVEY OF FOUR HUNDRED CASES OF CEREBRAL PALSY IN CHILDHOOD. PATRIA ASHER and F. ELEANOR SCHONELL, Arch. Dis. Childhood **25**:378 (Dec.) 1950.

Among 349 cases of congenital cerebral palsy there were 290 cases of spastic paralysis (83%), 36 of athetosis (10%), 17 mixed cases (5%), 3 cases of ataxia, 2 of flaccid paralysis, and 1 of rigidity and tremor. The relative incidence of spastic paralysis and athetosis is discussed, with special reference to the figures given in other published series.

The etiology of congenital cerebral palsy is discussed. Evidence from this series suggests that athetosis is usually the result of birth injury or asphyxia or of neonatal jaundice, whether due to Rh isoimmunization or not. Birth injury probably causes some cases of spastic paralysis, while others are the result of genetic or intrauterine factors.

All but two patients over the age of 3 years were examined by a psychologist and the intelligence was assessed in all but 14 cases, by the method of Stanford-Binet (T.M.L.). The I. Q. was 70 or over in 51% of cases, between 50 and 69 in 23%, and below 50 in 26%. No significant difference in the mean I. Q. of spastics and athetoids was found.

The mean I. Q. of the various groups varied inversely with the severity of the physical handicap; thus the mean I. Q. of spastic quadriplegics was significantly lower than that of the hemiplegics or paraplegics. An examination of the attainment in reading of the normally intelligent and bright children reveals a very considerable degree of retardation. This suggests that, unless special educational provision is made, many patients will lack the stimulus necessary to develop their capacities beyond mediocre levels.

KELLY, Milwaukee.

INFLUENZAL MENINGITIS IN THE STREPTOMYCIN ERA. C. G. ALDERMAN, Clin. Rep. Adelaide Child. Hosp. **2**:78 (May) 1951.

In four years 35 patients with influenzal meningitis and 3 with doubtful cases of the disease were treated, with seven deaths. All received specific antiserum, sulfadiazine, and streptomycin. Five patients were moribund on admission; so that results were better than before the use of streptomycin. Intrathecal therapy was used without prolonging the recovery.

McGUIGAN, Evanston, Ill.

SYMPOSIUM ON CEREBRAL PALSY. SOUTH AFRICAN M. J. **25**:816 (Oct. 20) 1951.

This symposium includes five articles. The first is a brief history of the Pretoria school for cerebral palsy. The following articles discuss the cause of cerebral palsy, psychological implications in assessing the mental ability of the child with cerebral palsy, treatment of cerebral palsy (the treatment is stated to be a form of brain training), and orthopedic treatment of cerebral spastics. This symposium is very brief, and none of the articles presents a new approach to the problem.

McGUIGAN, Evanston, Ill.

"HEALING" OF AN INFANT WITH PNEUMOCOCCUS MENINGITIS. CORNELIA DE LANGE, Ann. pædiat. **175**:235 (Sept.) 1950.

The case history and the anatomicopathological findings are given of an infant with pneumococcic meningitis, who after the acute phase of the illness became lethargic and continued in this condition for more than a year, i. e., till her death. A marked obesity developed.

The clinical symptoms and the histological findings were largely in accordance with what our knowledge teaches. The somnolence was explained by the destruction of the central gray matter round the aquaeductus Sylvii, the ophthalmoplegia externa totalis by the destruction of the oculomotor nerve nuclei, the divergence of the eyes at rest by the fact that the nuclei of the nervous abducens were unimpaired.

The obesity was accounted for by a sharply defined tuberitis caused by the spreading of a localized basal meningitis to the tuber and destruction of the ganglion cells. The considerable hydrocephalus externus and internus was not obstructive, the whole iter being passable. It probably depended on production of a large quantity of exudate by the ependyma and the plexus chorioidei, though it is not quite clear why resorption had not again set in after the cortex and the meninges of the brain convexity had healed. The nystagmus may be connected with the foci of destruction found in the corpora quadrigemina.

Clinically and histologically the process showed symptoms of a local recovery.

In the treatment of acute infectious meningitis the optimum certainly has not been reached. Lives are saved that formerly would undoubtedly have been lost, but the cerebral damage is a great drawback. In future it will be an advance if the intrathecal treatment is abolished and if in the intramuscular therapy depot penicillin is used.

FROM THE AUTHOR'S SUMMARY.

CISTERNA INTERVENTRICULARIS AND ITS CLINICAL IMPORTANCE. HANS ZELLWEGER, Helvet. pædiat. acta **6**:484 (Dec.) 1951.

Encephalograms and anatomical pictures of the interventricular cistern are presented. Up to now, the finding of an interventricular cistern in the pneumoencephalogram was interpreted erroneously as cavum vergae. The interventricular cistern is not filled through the ventricular system, as is cavum vergae, but by air flowing from the basal cistern via the cisterna ambiens to the cisterna venae magnae cerebri. An interventricular cistern overlying the splenium corporis callosi occasionally shows an indentation of its posterior margin corresponding to the caudal end of the splenium corporis callosi. No child with this encephalographic change was older than 19 months. The encephalographic finding of an interventricular cistern gives no information concerning etiology and nature of the underlying cerebral disturbances, although in three autopsies performed hypoplasia of the corpus callosum was found. Thirty patients with interventricular cisterns were observed, 24 of whom were low-grade morons, with a high mortality in early childhood; only one child was considered to be normal, and three others were rather slightly mentally retarded.

FROM THE AUTHOR'S SUMMARY.

MICROCEPHALY. LORENZO BIANCHI and SERGIO LEVI, Riv. clin. pediat. **48**:625 (Oct.) 1950.

The brain of a microcephalic girl of one year of age has been studied. The reduction of the dimensions of the neurocranium is attributed to the reduction of the encephalic mass; the dependence of the skull size on that of the encephalon and not vice versa is now definitely established, thanks to the studies of many authors. It has also been ascertained that the brain is the part of the encephalon presenting most alterations, the other parts undergoing modifications in consequence of cerebral alterations; the present study deals exclusively with the cerebral cortex. The gyri and sulci of the brain show simpler and more rudimentary arrangements than those of normal subjects. Features are found proper to normal man as well as aspects suggestive of the sulci found in the skulls of monkeys; this is true of many other cases documented in literature and is easily explained if we consider that the brains of all primates are constructed on a common pattern and that they differ only in degree not in quality. Therefore a human brain with a less extensive cerebral cortex must necessarily present monkey-like aspects, though this does not prove the possibility of atavism.

The cerebral cortex in this case has not shown any profound structural qualitative alterations. Many of its cells have normal aspects; others have abnormal aspects and arrests in development. In any case, the principal cortical areas are to be recognized by their essential structural characters. There is a remarkable diminution in the number of cells in all the cortex, particularly apparent in the granular and supergranular strata; this has been demonstrated by comparative methods.

Pathogenetic causes, the presumably determining causes of microcephaly, are mentioned and discussed; in the case here illustrated, the condition is ascribed to an indeterminate arrest of development, that is, to something which has prevented the normal process of cell multiplication. Therefore, though many elements have retained their normal formative activity (inasmuch as the cortex does not have a fetal aspects) a large reduction in the total quantity of cerebral cortex has ensued, making it impossible for the cortex to expand as much as its age would require.

FROM THE AUTHORS' SUMMARY.

TREATMENT OF MENINGITIS DUE TO STREPTOCOCCI, STAPHYLOCOCCI AND HEMOPHILUS INFLUENZA. R. RAMOS, Arch. pediat. **1**:53 (July) 1950.

Ramos outlines details of treatment for meningitis due to three types of causal organisms. He points out that foci of infection should be removed and that one should not merely trust the sulfonamides and antibiotics alone. For example, purulent mastoiditis may coexist with meningitis, and drainage as well as medical care should be considered.

The author gives the dosages for intrathecal, intravenous, and oral use of drugs and trade names of the best products available among the sulfonamides and antibiotics.

ALLEN, San Francisco.

EPILEPSY IN GENERALIZED FLEXION. HECTOR J. VASQUEZ and MARCOS TURNER, Arch. argent. pediat. **35**:111 (March) 1951.

The authors report 10 cases in which the clinical picture is sufficiently distinct to suggest the establishment of a "new epileptic syndrome." The attacks consist of a sudden, tonic flexion of the head and extremities, with loss of consciousness and fixation or wandering of the eyes, with or without a cry. Clonic movements are not observed. The attacks are very brief and frequent. Seven of the 10 infants had a definite history of birth trauma; an older sibling of another was an "epileptic." The onset was during early infancy in most of the cases. All the patients were markedly retarded. Pneumoencephalograms were made for 7 and were all grossly abnormal, with ventricular dilatation and cortical atrophy, and of no apparent diagnostic aid. Electroencephalograms were abnormal in nine with a predominant spike and dome pattern. Therapy with several of the well-known anticonvulsant preparations met with little success.

PANOS, Galveston, Texas.

Psychology and Psychiatry

SHORT TERM MANAGEMENT OF A CHILD BEHAVIOR DISORDER. VICTOR H. ROSEN and EVA LANDSBERG, Pediatrics **10**:484 (Oct.) 1952.

A seemingly obstinate case of refusal to be toilet-trained in a 4-year-old boy was treated by brief counseling of the mother. The interpretation of her own conflict was the major factor in the reversal of the child's problem. The rather striking results are discussed in terms of the parent-pediatrician relationship and the pediatrician-psychiatrist team work. The effect of bringing a psychodynamic point of view to bear in the elucidation of intrafamilial tensions is evaluated.

FROM THE AUTHORS' SUMMARY.

ABNORMAL ELECTROENCEPHALOGRAM AS RELATED TO READING DIFFICULTY IN CHILDREN WITH DISORDERS OF BEHAVIOR. MARGARET A. KENNARD, RALPH RABINOVITCH, and DONALD WEXLE, Canad. M. A. J. **67**:330 (Oct.) 1952.

Studies of electroencephalograms of 47 children with behavior disorders were made in order to ascertain possible correlation between abnormalities of the electroencephalogram and reading difficulty. It was found that no apparent relationship existed between disorders producing cortical dysrhythmia and those underlying reading difficulties.

McGUIGAN, Evanston, Ill.

TREATMENT OF PHENYLKETONURIC MENTAL RETARDATION : FÖLLING'S DISEASE. F. LOTTI, Clin. pediat. **33**:729 (Nov.) 1951.

Three children with Fölling's disease were studied. One child received 10 gm. of glutamic acid and 75 mg. of vitamin B_1 daily for six months. A second child received the same amount of glutamic acid but no added vitamin B_1. The third child served as a control. The medication led to no change in the amount of phenylketonuric acid secretion in the urine. The glutamic acid ingestion seemed to lead to some improvement in the mental capacity of the children, especially over the first three months; however, they still were definitely mentally retarded. No discernible benefit could be ascribed to the vitamin B_1.

HIGGINS, Boston.

Diseases of Genitourinary Tract

ADENOCARCINOMA OF THE TESTIS OCCURRING IN INFANTS: REPORT OF 2 CASES. D. MAGNER and A. J. S. BRYANT, A. M. A. Arch. Path. **51**:82 (Jan.) 1951.

The authors report two cases of testicular tumors occurring in a 10-month-old and a 22-month-old boy. The tumors invaded and enlarged the testis. On the basis of the histology, the diagnosis for each was adenocarcinoma of the testis. The authors believe these neoplasms to be a morphologically distinctive type and postulate a dysontogenetic origin from rete blastema.

HAW CHAN, San Francisco.

EXSTROPHY OF THE URINARY BLADDER. HARRISON C. HARLIN and CHESTER A. FORT, Brooklyn Hosp. J. **9**:132, 1951.

Technique of repair of exstrophy of the bladder is discussed in detail. The authors believe that ureterosigmoidal anastomosis should be carried out during the first few years of life.

McGUIGAN, Evanston, Ill.

NEW CONCEPTS OF THE ETIOLOGY OF MEGALOURETERS. ORVAR SWENSON, H. EDWARD McMAHON, WILLIAM E. JAQUES, and JAMES S. CAMPBELL, New England J. Med. **246**:41 (Jan. 10) 1952.

The authors state the present concept of Hirschsprung's disease, that there is an absence of peristalsis in the rectosigmoid. This deficiency is in turn thought to be due to the congenital absence of mesenteric ganglion cells and is thought to produce consequent dilatation and hypertrophy of the proximal colon.

The associatien of megalobladder and megaloureter with megacolon has been reported; the authors found that 12 of their patients with megacolon had abnormally increased bladder capacity. In addition they studied three patients with bilateral megaloureter and one with unilateral megaloureter in an effort to produce evidence that faulty innervation of the bladder may exist as an isolated defect or as an associated defect with megacolon. They postulate that the former abnormality produces patients with megaloureters.

Pathologic studies of normal and abnormal ureters and bladders were carried out, and the histologic results described. These would tend to support the authors' hypothesis that diminution of parasympathetic ganglion cells in the bladder may be the fundamental lesion in the megalobladder associated with Hirschsprung's disease and in megalobladder which produces megaloureter.

WHEELOCK, Denver.

BLOOD UREA CLEARANCE IN NORMAL BABIES AND IN THOSE WITH NEPHROPATHY. G. PASSARO and M. BARBATI, Arch. ital. pediat. e puericolt. **14**:135, 1950.

The author has studied blood-urea clearance in normal children and in children with renal disease.

In 68 healthy children the values for standard clearance corresponded to those established by most authors for adults. Expressing renal function in percentages gives a better valuation of the damaged kidney.

The test allows one to follow the evolution of the nephropathy, showing the smallest variations in renal failure, and to formulate a prognosis, particularly in subacute and chronic forms. This test is indubitably superior to other functional tests, being less influenced by extrarenal factors.

FROM THE AUTHORS' SUMMARY.

CONGENITAL PARARENAL TUMOR (SYMPATHOGONIOMA) IN A PREMATURE INFANT. C. M. PINTOS, E. A. FRUGONI, and M. R. LLAMBIAS, Arch. argent. pediat. **34**:49 (July) 1950.

A premature infant weighing 1,700 gm. presented a small, firm tumor mass in the left upper abdominal quadrant; the mass moved with respiration but had a lumbar attachment. At surgery, it was so adherent to the renal structures that a left nephrectomy was performed. Subsequent dissection proved the tumor to be separate from the adrenal gland and kidney. Autopsy revealed no site of metastasis.

PANOS, Galveston, Texas.

STUDIES OF THE RENAL EXCRETION OF P^{32} IN INFANCY AND CHILDHOOD. LARS STROM, Acta pædiat. **40**:88 (May) (Supp. 82) 1951.

The purpose of the present investigation was to study the renal excretion of a labeled phosphorus compound in normal and pathological conditions and to examine the possibility of using the values of the exchange between plasma orthophosphate and urine orthophosphate as a renal function test. A comparison between this test and other commonly used renal tests was made in one group.

The first chapter is a very short survey, or rather a résumé, of the literature on the development of renal physiology. A special section in this chapter is given to renal phosphate excretion.

In the next chapter the use of radioactive isotopes in general and the use of radioactive phosphorus in particular are discussed. The safeguards for the use of isotopes in human beings are emphasized.

The renal excretion of P^{32} was studied in a total of 101 persons, 96 infants and children and 5 adults. Of these, 28, including the 5 adults, were premature and 63 represented various diseases affecting the kidneys. The 28 normal subjects were used as a control group.

The investigations were performed on hospitalized children. The technical procedure is described in the third chapter. The determinations of orthophosphate in blood and urine were carried out according to a routine method used at the Wenner-Gren Institute, specifically the Fiske-Subbarow method with Brigg's modification as described by Lindberg (1946). The determination of radioactivity was also performed according to the routine methods of this institute.

After an intravenous injection, P^{32} can be found in the urine after about five minutes. The excretion of P^{32} increases, in the course of the first hour, to considerable amounts as compared

with the activity of the blood; after about 20 to 40 minutes the specific activity is higher in the urine than in the blood. This is in complete agreement with the results of the other investigations, which, however, were carried out mainly in animals. The fact that the specific activity of urine is higher than that of blood has been discussed.

In patients with renal disease, which was acute glomerulonephritis in nearly all these cases, the excretion of P^{32} is altered from the pattern found in children with normal renal function. The specific activity of the urine is lower than that of the blood plasma. The decreased specific activity of the urine in disease is apparently due to a disturbance of renal metabolism.

In premature infants the specific activity in the urine is much lower than that of blood plasma. They, like children with glomerulonephritis, show very low phosphate clearances.

In a special chapter an account is given of diabetic children, all treated with insulin and a free diet. In those cases the inulin and the paraaminohippuric acid clearances were also determined. No significant correlation between the clearance values and the P^{32} excretion could be stated. A decreased specific acivity of the urine was found in a patient with acidosis, who on another occasion showed a normal P^{32} excretion. In two cases of diabetes in which the duration of the disease was 8 to 10 years, the urine was of low specific activity, although these children did not show any clinical signs of nephropathy. It is suggested that the determination of the relation between the specific activity in the urine and in the blood might be a more sensitive test of early renal disturbance than those now commonly employed.

FROM THE AUTHOR'S SUMMARY.

TRIDIONE IN NEPHROSIS. W. H. H. TEGELAERS and H. TIDDENS, Maandschr. Kindergeneesk. **20**:23 (Feb.) 1952.

After a review of the literature a report is given on a boy aged 7, in whom a nephrotic syndrome developed one year after the beginning of treatment of petit mal with trimethadione. The blood chemistry and urea and creatinine clearance figures indicate that glomerular function was initially damaged. Treatment resulted in complete cure.

FROM THE AUTHORS' SUMMARY.

Diseases of Ductless Glands; Endocrinology

FUNCTIONAL RELATIONSHIP BETWEEN THE ADRENAL CORTEX AND POSTERIOR PITUITARY. C. SUSAN NAGAREDA and ROBERT GAUNT, Endocrinology **48**:560 (May) 1951.

It is suggested on the basis of this and other work that, while the major endocrine factor in the elimination of a small excess of body water is a suppression of secretion of the posterior pituitary antidiuretic hormone, a larger water load causes, in addition, increased adrenocortical hormone secretion, augmenting the diuretic response. The hypothesis is stated, but not proved, that integration of posterior pituitary adrenocortical activity may be achieved in hydrated states by both glands being responsive, in a inverse manner, to changes in the osmotic pressure of plasma.

JACOBSEN, Buffalo.

PROGERIA (HUTCHINSON-GILFORD SYNDROME): REPORT OF A CASE AND REVIEW OF THE LITERATURE. JAMES THOMSON and JOHN O. FORFAR, Arch. Dis. Childhood **25**:234 (Sept.) 1950.

A classic case of progreia is described. The world literature relating to this subject is reviewed, and it is concluded that this is the 19th typical case to be reported. Approximately as many atypical cases have been described, and a separate grouping and naming of these is advocated. The clinical features, diagnosis, pathology, and treatment of progeria are discussed. It is suggested that dysfunction of the anterior lobe of the pituitary, possibly of the eosinophile cells, is the underlying lesion.

KELLY, Milwaukee.

A CASE OF SPORADIC CONGENITAL GOITRE. A. L. D'ABREU and B. S. B. WOOD, Arch. Dis. Childhood **25**:235 (Sept.) 1950.

A case of sporadic congenital goiter causing severe respiratory embarrassment is described. Despite intensive treatment with both thyroid extract and iodine, surgical relief became

necessary. The histological findings in the thyroid gland at various stages of oral thyroid administration are described. The literature is briefly reviewed, and the management of such cases is discussed.

KELLY, Milwaukee.

ACTION OF THE SEX HORMONES ON HEMOPOIESIS. G. CARDINI and M. VERROTTI, Clin. pediat. **32**:685 (Dec.) 1950.

Ten boys, 10 to 24 months of age, were given 10 daily injections of 5 mg. of testosterone propionate; this treatment led to an increase in leucocytes and a decrease in lymphocytes of the peripheral blood and to an increased activity of the granulocytic cells of the bone marrow but not to any change in the degree of maturation of these cells. Practically identical findings were observed when 10 daily injections of 0.5 mg. of diethyldioxystilbene were given to 10 girls in the same age group. It appears that the injections of the hormones had the same effect on the granulocyte-lymphocyte ratio in the blood picture of these young children as appears later in adolescence with the increased physiological activity of the sex glands. Progesterone injections were observed to have no effect on hemopoiesis.

HIGGINS, Boston.

MAURIAC SYNDROME IN THE DIABETIC CHILD. A. WINDOFER, Deutsche med. Wchnschr. **76**:1583 (Dec. 14) 1951.

The author adds the case of a 9-year-old girl to the 37 of the Mauriac syndrome reported in the literature. Severe diabetes in children, apparently with difficulties in its control by insulin, is associated with cessation of growth in length or with diminution of growth, and with a pronounced hepatomegaly due to fatty infiltraton or to glycogen deposition. The glycogen is subject to autolysis. Results of functional tests of the liver are within normal limits. In addition, such children may present fat depositions on face and trunk, while the extremities remain free. The relationship of this syndrome to diabetes and to glucogenosis is discussed. All three conditions arise in consequence of a faulty regulation of hormonal equilibrium, disturbing the balance of insular and contrainsular factors, centering in the hypophysis.

AMBERG, Rochester, Minn.

ADRENAL-FUNCTION TESTS IN CHILDREN. F. SOUCHON, Ztschr. Kinderh. **67**:179, 1949.

The results of water tests in 100 children showed that about one-third of the children had temporary positive tests following infectious disease. The test consists of two parts: (1) a quantitative evaluation of the water elimination before and after a large measured amount of water intake, and (2) a comparison of the blood and urine urea and chlorides according to a mathematical formula.

The author considers the findings of the water test more reliable in the determination of a possible adrenal-cortex insufficiency than other examinations and feels that prolonged rest during convalescence and perhaps even specific therapy are indicated in cases with a positive test.

GLASER, Jerusalem.

URINARY EXCRETION OF NEUTRAL 17-KETOSTEROIDS DURING TREATMENT WITH CORTICOTROPIN (ACTH). E. DINGEMANSE and L. G. HUIS IN 'T VELD, Nederl. tijdschr. geneesk. **94**:2182 (July 29) 1950.

Patients to whom corticotropin has been administered excrete increased amounts of 17-ketosteroids in the urine. Some days after institution of this therapy the 17-ketosteroid excretion is fixed at a stable level; after prolonged treatment with the same dose of corticotropin, the excretion decreases. Distribution of the dose of corticotropin over several injections brings about a greater 17-ketosteroid excretion than does administration of the same dose in a single injection. This fact was first discovered in one of the patients reported on by van Creveld and Kuipers (*Nederl. tijdschr. geneesk.* **94**:2175, 1950), who received a daily dose of 25 mg. of corticotropin. On a regimen of 2.5 mg. four times a day, the 17-ketosteroid excretion was the same as when 25 mg. was given in one injection.

The composition of the 17-ketosteroid mixture in the urine of patients treated with corticotropin corresponds to that typical for patients with Cushing's disease.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

CONGENITAL DYSPLASIA OF THE HIP JOINT IN EARLY INFANCY. RICHARD D. HAWKINS, South. M. J. **45**:18 (Jan.) 1952.

This is an article written by a pediatrician for those doing general or pediatric practice. It contains a review of the literature. The specific points of diagnosis are tabulated and further illustrated by diagnosis and reproductions of x-ray films. The author emphasizes the necessity of making the diagnosis during the early weeks of life. He reports six cases, in two of which the diagnosis was made during the first 12 hours of life, in two before 6 months of age, and in two before 9 and 21 months, respectively.

LOGAN, Rochester, Minn.

HYPERTROPHY OF THE LOWER LIMBS WITH CUTANEOUS NAEVUS AND VARICOSE VEINS. L. M. ROSE, Arch. Dis. Childhood **25**:168 (June) 1950.

Rose describes a case of enlargement of both lower limbs associated with an extensive cutaneous nevus and varicose veins in a boy aged 7 years.

There was little evidence in favor of there being a congenital arteriovenous communication in either lower limb. No thrills or bruits were detected. The blood pressure in the two lower limbs was the same and not abnormally raised. There was no cardiac enlargement. There was no bradycardiac response on occlusion of each femoral artery. The oxygen content of the venous blood from the right lower limb was normal. An arteriogram showed no evidence of an abnormal arteriovenous communication in either limb.

FROM THE AUTHOR'S SUMMARY.

SPECIAL TECHNIQUE FOR TREATMENT OF A CASE OF COXITIS WITH STREPTOMYCIN. P. E. CARRAI, Riv. clin. pediat. **49**:910 (Dec.) 1951.

Excellent results have been obtained by the author by use of streptomycin in a case of coxalgia, predominantly located in the innominate bone. The streptomycin is introduced from the inside of the pelvis and passed with a long needle through the foramen obturatum. This method is advised for similar cases.

FROM THE AUTHOR'S SUMMARY.

EARLY DIAGNOSIS OF CONGENITAL DISLOCATION OF THE HIP. EUGENIO DIAZ BORDEU, Rev. chilena pediat. **22**:558 (Dec.) 1951.

The author studied 317 children with congenital dislocation of the hip. The prognosis is better if treatment is begun before the first year of age. The initial symptoms were in order of frequency, a tendency to external rotation of an extremity, shortening of a leg, crepitation and noises at the hip joint, other congenital defects of the legs, and asymmetry of the inguinal folds. The diagnosis in infancy is a clinical one, established when one can demonstrate the passing of the head over the socket edge of the acetabulum, a sign that is 100% positive in infants under 6 months of age. The technique of this examination is described.

FROM THE AUTHOR'S SUMMARY.

HALLUX RIGIDUS IN THE CHILD. EUGENIO DIAZ BORDEU, Rev. chilena pediat. **22**:562 (Dec.) 1951.

The author studied 12 cases of hallux rigidus in children under 15 years of age. He describes the symptomatology and proposes as therapy muscular section, with which he has obtained excellent results in all his cases.

FROM THE AUTHOR'S SUMMARY.

INFLUENCE OF IMPLANTATION OF THYROID GLAND TISSUE IN RHEUMATIC AND OTHER JOINT DISEASES. F. MANDL and W. GYRI, Wien. klin. Wchnschr. **63**:916 (Dec. 7) 1951.

In 36 cases of various forms of arthritis or arthrosis the results of implantation of preferably fresh thyroid gland were so beneficial as to invite further study.

AMBERG, Rochester, Minn.

CLINICAL OBSERVATIONS OF CRANIOTABES: MATERIAL FROM TWO CHILD WELFARE STATIONS IN COPENHAGEN. KAREN BLOM, Ugesk. læger **112**:1326 (Sept. 21) 1950.

Of 662 infants belonging to two infant welfare centers from Oct. 1, 1947, to Oct. 1, 1948, there were 12.6% who displayed craniotabes without other rachitic signs. Craniotabes was more frequent in breast-fed infants. Of the infants with craniotabes, 8.4% were premature; of the other infants, 4% were premature.

WALLGREN, Stockholm, Sweden.

EFFECT OF ACTH THERAPY ON SEROLOGICAL REACTIONS IN RHEUMATOID ARTHRITIS. P. E. VAN LOGHEM-LANGEREIS and J. J. VAN LOGHEM JR., Nederl. tijdschr. geneesk. **94**:2254 (Aug. 5) 1950.

The influence of administration of corticotropin (ACTH) on serological reactions of six patients with rheumatoid arthritis was investigated. The antistreptolysin titer, anti-H and anti-O agglutinin titers, and the Rose test titer were determined. A modification of the Rose test was used. In all patients a decrease of the four titers was noted during administration of corticotropin. The authors assume that the decrease of the titers can be ascribed to a nonspecific decrease of the gamma globulin content of the serum.

VAN CREVELD, Amsterdam, Netherlands.

Cutaneous Diseases; Allergy

SUBCUTANEOUS BERYLLIUM GRANULOMA. SEYMOUR B. SILVERMAN and CYRUS C. ERICKSON, Arch. Path. **50**:63 (July) 1950.

The case of a 12-year-old white boy is reported. The boy sustained a nonhealing laceration of the hand two years after injury from handling a broken fluorescent lighting unit. The scar was excised, and the patient recovered uneventfully. Histologically the lesion was of interest because of its marked similarity to the Darier-Roussy type of Boeck's sarcoid. The authors give a few differential points in the histological features in distinguishing the two lesions from each other, but the pictures are not always clear-cut. Even though spectrographic analysis of a fragment of the original material of this reported case revealed no beryllium, the authors conclude that the history, clinical course, and histological appearance of the lesion are so characteristic of the subcutaneous beryllium granuloma that one cannot escape the conclusion that this is indeed an example of such a lesion.

HAW CHAN, San Francisco.

ECZEMA IN INFANCY AND CHILDHOOD. LEWIS W. HILL, New England J. Med. **242**: **286**: (Feb. 23) 1950.

The author presents a precise analysis of current thought in regard to eczema of infancy and childhood. These two articles should be read carefully by anyone interested in this difficult problem of allergy, despite the discouraged tone of the author's summary, which follows:

"In the last four years little progress has been made in the study and treatment of eczema in infants and children. It is still treated much as it has been for the last twenty years—no spectacular cure it at hand. The antihistaminic drugs have not contributed much, and unsaturated fatty acid therapy has not yet become standard.

"There has, however, been a greatly increased interest in this disorder, and most of those who are particularly concerned with it write profusely, so that there has been a considerably greater dissemination of what facts are known, which has probably brought about generally better treatment.

"Original investigations that have added to existing knowledge have been few. Rowe's studies on pollen dermatitis, Wolpe's observations on low serum protein and the work that has been done by several individuals and 'teams' on Kaposi's varicelliform eruption represent about the only new and original contributions. To quote R. A. Cooke 'Allergic dermatitis is today, I think, the number one problem child of allergy. What is neded is more light and a new approach.'"

WHEELOCK, Denver.

A REVIEW OF INFANTILE ACRODYNIA (PINK DISEASE). DUNCAN LEYS, Arch. Dis. Childhood **25**:310 (Sept.) 1950.

A study of published cases of acrodynia and the personal experience with a further 31 cases leads the author to the conclusion that this disease of infancy and early childhood should be regarded as a form of encephalopathy; the complex clinical picture can be satisfactorily explained by disturbed function of the hypothalamus, and the term "diencephalopathy" is suggested as a convenient descriptive term. The cause is still unknown, and the possibility that this may be a primary emotional disorder is discussed. Attention is called to symptomatic resemblances between acrodynia in the infant and neurodermatomyositis in the adult.

KELLY, Milwaukee.

STEVENS-JOHNSON SYNDROME: REPORT OF TWO CASES TREATED WITH AUREOMYCIN. L. J. A. LOEWENTHAL, J. L. B. MARAIS, and H. D. RUSKIN, South African M. J. **24**:686 (Aug. 19) 1950.

Two patients with Stevens-Johnson Syndrome were treated with aureomycin, treatment beginning on the eighth day of the disease. Both patients were out of danger in two days. Treatment was continued for 10 days.

MCGUIGAN, Evanston, Ill.

APPEARANCE OF HYPERTRICHOSIS DURING STREPTOMYCIN TREATMENT. RENÉE FONÓ, Ann. pædiat. **174**:389 (June) 1950.

Twenty-seven children (15 boys and 12 girls) with miliary tuberculosis and tuberculous meningitis were treated with streptomycin. Twenty-two showed a hypertrichosis after six to eight weeks of treatment. The hypertrichosis begins generally on the upper side of the limbs and spreads successively over most of the body.

It has not been possible to ascertain the cause of hypertrichosis by simple observation. Possibly, it develops under the specific influence of streptomycin or as the result of the disease itself when it has become chronic, and the only effect of streptomycin is that the child's life is preserved.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF SEBORRHEIC DERMATITIS AND ECZEMA IN INFANTS WITH CHOLINE. R. BIAGINI, Clin. pediat. **33**:631 (Oct.) 1951.

Ten children (1 month to 4 years of age) with eczema and 2 with seborrheic dermatitis showed marked improvement clinically and by laboratory tests after treatment with choline (0.50 to 0.75 gm. daily divide into four doses) over a period of 15 days. Six normal children of similar ages showed an average of 381 mg. of unsaturated fatty acids per 100 cc. of blood; 8 of 9 of the eczematous patients had 160 to 274 mg. of unsaturated fatty acids per 100 cc. of blood before and 218 to 288 mg. after the treament. There was a tendency of the blood cholesterol to show a slight rise after the choline treatment.

HIGGINS, Boston.

XERODERMA PIGMENTOSUM. DARIO SEPULVEDA R., Rev. chilena pediat. **21**:321 (July) 1950.

The author reports the case of a 5-year-old girl with the characteristic signs of xeroderma pigmentosum with a certain degree of mental deficiency. There was no history of consanguinity, although there was a positive history of epilepsy. The author stresses this fact because he has found this association with greater frequency than consanguinity in several cases of congenital dermatoses (ichthyosis) in which the classical authors mention only the frequency of consanguinity.

FROM THE AUTHOR'S SUMMARY.

Books

Management of the Newborn Infant. By Arthur H. Parmalee, M.D. Price, $7. Pp. 358, with 47 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1952.

The newborn infant has become a steadily increasing subject of interest in many areas of medical thought. Health authorities are concerned because little progress has been made in reducing mortality in the neonatal period, particularly the first two days of life. Physiologists are just beginning to appreciate that here lies a great unexplored field for research which promises most rewarding results. Psychologists and psychiatrists have begun to realize that patterns of behavior and conduct begin to be formed from the very beginning of life and that child-parent relationship, even in the newborn phase, may have great bearing on subsequent emotional adjustment.

This book, coming as it does from the long and extensive experience of the author, and with its practical approach to the newborn infant both as a normal and an abnormal individual, is accordingly most timely. While it professes to deal only with subject matter from the author's personal experience, there are few conditions which occur in the newborn period which are not covered.

The long and detailed chapter on the characteristics of the normal newborn infant is particularly good and of itself would warrant the attention of all persons dealing with babies.

The style is exceedingly clear and intimate and free of technical language, which makes it suitable as a text for students and nurses without lessening its usefulness for physicians.

The recommendations for treatment are for the most part conservative, which of course reflects the influence of the long experience and observation of the author.

This is a most valuable addition to pediatric literature in bringing various aspects of this important subject together under one cover. It will prove most useful both as a reference book and as a text.

Textbook of Clinical Parasitology. Edition 2. By David L. Belding, M.D. Price, $12. Pp. 1,139, with 283 illustrations. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York 1, 1952.

As stated, this volume is a textbook which is fairly complete and presented in a well-organized and readable form. The book is divided into seven sections covering the general headings of General Parasitology, The Protozoa, The Nemathelminthes, The Cestoidea, The Trematoda, The Anthropoda, and Technical Methods for the Diagnosis and Treatment of Parasitic Infections. There is an index of authors and an index of subjects.

All organisms are classified and the morphology and physiology are discussed.

Each disease entity is well described, with the history, distribution, morphology and physiology, and characteristics of the particular causative organisms elaborated upon. The transmission of the disease, the pathogenicity, the pathogenesis, the clinical course, the diagnosis, and the treatment are well covered in each instance.

The last section, on "Useful Drugs in the Treatment of Parasitic Diseases," is a most interesting and up-to-date compendium.

This text would be an ideal reference for those interested in the diseases caused by parasites.

Your Child Can Be Happy in Bed. By Cornelia Stratton Parker. Price, $2.95. Pp. 275, with illustrations by Heda Teitcher. Thomas Y. Crowell Company, 432 4th Ave., New York 16, 1952.

This is a book which should be invaluable to the mother of small children. It is packed with suggestions to keep a child busy and happy, whether he be bedridden or merely bored. There are chapters on practically every conceivable subject pertaining to the amusement of a child. Suggestions on what to do or make, how to do it, materials needed, and even on just plain talk are so numerous as to satisfy the needs of any harassed mother. There are lists, many outlined

by ages, on ways to amuse a child in bed, toys to buy, suggestions for interesting reading, gifts for children to make, catalogues of children's books, information on children's magazines, and recipes. The final chapter discusses making it easier to care for a child in bed.

This book should be a must for every mother. Those who buy it will never regret it.

The Auricular Arrhythmias By Myron Prinzmetal, M.D.; Eliot Corday, M.D.; Isidor C. Brill, M.D.; Robert W. Oblath, M.D.; H. E. Kruger, and associate authors. Price, $16.50. Pp. 387, with 323 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1952.

This book, "The Auricular Arrhythmias," is not a textbook, but is the result of five years of team-work of five authors and eight associate authors on the mechanism, clinical manifestation, and treatment of the following auricular arrhythmias: premature systole, tachycardia, flutter, and fibrillation. During the past 30 years, most of the work on the mechanism of these arrhythmias has been dominated by the brilliant experiments of Sir Thomas Lewis, whose circus-movement theory appeared very convincing to most investigators.

Dr. Prinzmetal and his co-workers made use of a high speed cinematograph that could take motion pictures of the auricles at rates varying between 500 and 3,000 frames per second; thus they were the first ones to record the exact mechanical events of the wave of contractions of the auricles. The use of the dual-beam cathode-ray oscillograph, which records the electrical activity of the auricles over 1,000 times that provided by the standard electrocardiograph, was another great help in further elucidating the knowledge of the electrical activities of the auricles in these arrhythmias.

Using a wider operative technique that enabled the authors to fully expand the left and right auricles, these authors produced various auricular arrhythmias on 300 dogs by means of electrical stimulation, the application of 0.05 to 5% solution of aconitine or direct application of heat or cold to the auricles. In man they studied 500 selected electrocardiograms with auricular arrhythmias, as well as many spontaneous arrhythmias, and in 18 human subjects they experimentally produced arrhythmias during thoracic surgical procedures. Records of these arrhythmias were taken on the multiple-channel electrocardiograph, and in some instances high speed cinematographs were recorded of the right auricle in man.

The material is divided into 18 chapters and an appendix. Each chapter is profusely illustrated, and although a great deal of technical matter is included, the subject is presented in clear simple language, and the summary at the end of each chapter is very appropriate. The plates, including the colored ones, are excellent, and apparently nothing has been spared by the publisher to make this as easily readable as possible.

The main conclusions that the authors have drawn from their numerous experiments are as follows:

1. Contrary to the view held by most workers, the wave of contraction of the auricles does not originate in the head of the sinoauricular node, but about 1 cm. to the right of the head, i. e., halfway between the head and tail of the sinoauricular node. The relaxation wave begins in the same region at which the contraction wave was originated.

2. Although the body and the appendix of the right auricle contract vigorously, the body of the left auricle shows practically no movement during systole. It serves as a conduit and not as a contractile organ. It is the appendix of the left auricle that contracts vigorously.

3. The principles that were found true in dogs apply equally well to human subjects.

4. Current methods of interpreting electrocardiograms in regard to differentiation between the various auricular arrhythmias are unsound and confusing.

5. The results of the cinematographic observations prove conclusively that there is no circus movement in the production of auricular paroxysmal tachycardia, flutter, or fibrillation. No evidence of a narrow "mother" path or of "daughter" waves were seen. When the ectopic focus was established at the caudal end of the interauricular septum, the auricles appeared to beat simultaneously. This phenomenon is compatible with Sir Thomas Lewis' theory of the circus movement and the unidirectional course hypothesized by him.

6. The Wolff-Parkinson-White syndrome is not due to anomalous A-V pathways, since it can be produced experimentally by stimulation of various sites in the ventricles, or by clamping

the venae cavae. The term "impure flutter," "flutter fibrillation," or "coarse fibrillation" is misleading. It is really auricular flutter with ventricular aberration.

7. The beneficial effects of digitalis and quinidine sulfate on auricular arrhythmias can be explained without resort to circus movement.

8. The nature of all arrhythmias is unitary. All auricular arrhythmias can be produced experimentally by electrical, chemical, or mechanical stimulation setting up an ectopic focus at a given site. The rate of discharge of stimuli from the ectopic focus determines the type of arrhythmia. The slowest stimulation resulting in 50 to 100 shocks per minute results in a premature auricular systole. A shock of 150 to 300 will bring on auricular tachycardia, a stimulation of 300 to 400 per minute, and auricular flutter, and a shock of up to 600 per minute will result in an auricular fibrillation.

This book is highly recommended to all teachers, investigators, and serious students of cardiology. It is well written, well documented, and adds a great deal to our knowledge of a controversial, and not too clearly understood, subject.

Let's Have Healthy Children. By Adelle Davis. Price, $3. Pp. 314, with 18 illustrations and 1 table. Harcourt, Brace and Company, Inc., 383 Madison Ave., New York 17, 1951.

This book is chiefly concerned with diet and eating problems. In the back of the book there is a table on food analysis. The book is interestingly written and is easily read. Dietary advice is given for pregnancy and the lactation period and for the baby at different ages. The point is made that both parents should be on a well-balanced diet before conception.

The reviewer believes this is a valuable book, especially as a reference book for the home.

Infant Development: The Embryology of Early Human Behavior. By Arnold Gesell, M.D. Price, $3.50. Pp. 108, with 18 illustrations. Harper & Brothers, 49 E. 33d St., New York 16, 1952.

This little book of 108 pages, including index and 18 pages of good photographs, represents the author's attempt to orient the psychologist, the pediatrician, or anyone working with children to the developmental approach to all supervision of infants and children, an end to which the author has devoted his life. The reader who is familiar with the writings and the cinema of this prolific author may be bored with the wordiness of the first seven chapters which say that "ontogeny recapitulates phylogeny." The eighth chapter discusses the clinical application of the developmental diagnosis and suggests that a brief inventory of the developmental status can be routine even in a busy pediatric practice. In the last chapter the author makes a noble plea that a developmental philosophy should become an integral part of our way of life.

Introduction to Medical Science. By Julius Jensen, Ph.D., M.R.C.S., L.R.C.P., and Henry W. Noller, M.D. Price, $5.75. Pp. 518, with 71 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1952.

"Introduction to Medical Science" by Jensen and Noller is a very interesting and well-written book. Much of the content is a short general review of various courses which most student nurses have in their preclinical period. A few examples of these courses are bacteriology, physiology, chemistry, nutrition, and nursing arts.

This book, however, could well be used as a supplementary text and would be an excellent means of review for medical science. Many important points are emphasized in such a way that it would be helpful in integrating courses and in determining relationships of all the material covered in the various courses.

Unit IV, How The Doctor Makes The Diagnosis, would be particularly helpful since diagnostic procedures and their significance are treated in detail. The quick reference section of laboratory procedures giving a wealth of information in condensed form is excellent.

Unit VI, How Disease Is Controlled and Prevented, brings together much valuable information in such a way that students would be able to better understand the breadth of federal, urban, and rural programs which have as their goal more safe and healthful living.

The glossary is fairly extensive, and the review questions, projects, and references all contribute to the value of the book.

Modern Medication of the Ear, Nose, and Throat. By Noah D. Fabricant, M.D. Price, $5.75. Pp. 245, with 20 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1951.

Since this volume covers a rather extensive field in only 245 pages, it must be somewhat sketchy and perhaps dogmatic. The author seems, however, to have chosen well the essentials of treatment along with adequate, though concise, discussions of underlying anatomy and pathology and sufficient reference to document his statements. He has weighed well the use of newer remedies in the light of older concepts, and few men familiar with the field will find much disagreement with his conclusions. Minor points such as only cursory reference to allergy in relation to recurrent sinus disease and the advice to use sprays of liquid petrolatum in the larynx may be questioned.

The text is well written, and the format and arrangements excellent. This book should have considerable value not only to the otolaryngologist but also to pediatricians and others whose fields overlap that specialty.

Health Observations of School Children: A Guide for Helping Teachers and Others to Observe and Understand the School Child in Health and Illness. By George M. Wheatley, M.D., M.P.H. Third Vice-President, Health and Welfare, Metropolitan Life Insurance Co., and Grace T. Hallock. Edition 1. Price, $4.75. Pp. 491, with 86 figures and 21 tables. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 18, 1951.

Everyone interested in the health of the school child recognizes the fact that the teacher, who is in close contact with children for one-third of their waking hours during 12 of their most formative years, is in a key position to make day-to-day observations of their growth and development and of the state of their health. The fact that most teachers are not adequately trained in health observation has been a weak spot in the effective utilization of the services of physicians, nurses, and other professional persons available for the maintenance and improvement of the health of the school child. An authoritative and comprehensive book such as this one, which offers basic and thorough training in health observation to any intelligent and alert lay person, is long overdue.

The early chapters give a three-dimensional view of the child, both as an individual and as a growing organism, presented on a sound physiologic and anatomic basis. With this, there are specific exercises for developing powers of observation. The following chapter gives a well-outlined description of the child's thoughts, feelings, and behavior patterns, both normal and abnormal, again on the basis of the physiologic functions of his nervous and endocrine systems. The succeeding chapters deal with the circulatory, respiratory, and gastrointestinal systems, the skin, eyes, ears, bones, and muscles. In all of these chapters a physiologic approach is maintained, and the fundamental facts are interpreted as they apply to the health needs of the school child. For example, following an excellent and nontechnical description of the organs of speech, there are tables on how consonant sounds and vowel sounds are formed, which are simple, basic and comprehensive. Similarly, the description of the anatomy and functions of the gastrointestinal tract is followed by tables on physical signs related to the general nutritional status, good food sources of specific nutrients, consequences of insufficient intake, etc.

There is an abundance of illustrations and colored photographs, and other graphic material, all of which are of high quality and show a remarkable degree of nontechnical interpretation. At the end of each chapter a "self quiz" section and a bibliography add to the value of the book as a text and as a reference work. The last section consists of a directory of resource organizations for health education material and a most comprehensive chapter-by-chapter list of available motion pictures and film strips.

The expressed purposes of the book are to help teachers and other lay persons to understand the physiologic basis of the signs and symptoms of disorders and defects prevalent among school children, to enable them to recognize these signs and symptoms, and to see that they are reported to the proper medical authorities as accurate observations without any reference to diagnosis. The book not only fulfills these purposes, but it goes farther. It will enable an interested teacher to supply a vital link by serving as a health educator in interpreting to the parents and the school authorities the significance of her observations and of the medical recommendations which result

from her referrals. Anyone reading the book must recognize that the type of training which it will afford the teacher will lead to closer and much-needed cooperation between teacher, nurse, parent, and physician.

The value of the book is not limited to nonmedical persons. It will serve the physician working in the schools, and it will help in orienting the medical student in his studies in community health. To cite one of many examples of this, a chart of the common acute diseases of children classified in terms not of morbidity percentages, but as causes of absence in terms of per cent of school days lost, is an illuminating and realistic point of view for the young physician.

It is to be hoped that medical schools and teachers' colleges, as well as teachers and practicing physicians, will recognize the value of this book in their curricula and libraries.

The Prevention of Rheumatic Fever. By Lowell A. Rantz, M.D. Price, $2.25. Pp. 66, with 5 tables and 1 figure. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1952.

The author introduces his subject by presenting the evidence for the etiologic role of the hemolytic Streptococcus in the production of the rheumatic state. He then considers the means whereby streptococcal infection can be avoided and the management of streptococcal infection once it has occurred. He emphasizes the early and vigorous treatment of streptococcal infections with penicillin as a means of preventing recurrences in known rheumatic patients. The long term prophylaxis of recurrences of rheumatic fever by the use of sulfonamides and penicillin is discussed.

This excellent little monograph sets forth in clear and concise form the present means at our disposal for the prevention of rheumatic fever.

First Report on Institutional Research Grants of the American Cancer Society. Price, not given. Pp. 258. American Cancer Society, Inc., 47 Beaver St., New York 4, 1951.

Committee on Growth of the National Research Council, Fifth Annual Report to American Cancer Society, Inc., July 1949-June 1950. Price, not given. Pp. 384. Division of Medical Sciences, National Research Council, 2101 Constitution Ave., Washington 25, D. C.

These two reports complement each other and should be read concurrently to appreciate the great scope of the research program initiated in 1947 by the American Cancer Society and supported by that organization.

Of all funds collected by the Society, 25% are alloted to research in three general groups: (1) fellowships, (2) grants-in-aid, and (3) institutional research grants.

Fellowships.—Three types of fellowships are awarded: The American Cancer Society Fellowship; the British American Exchange Fellowship, and the Damon Runyon Clinical Research Fellowship. The total of new fellowships awarded between 1947 and 1951 was 187. The applications for these fellowships have risen from 47 in 1946 and 1947 to 137 in 1950 and 1951. The policies governing the methods of awarding them—graduate degree requirements, geographical distribution (by state or country of applicants), origin of the applicant, and eventual location of practice proposed are detailed. A further grant designed for scholars in cancer research which is to aid young scientists will be available in 1951 and 1952. This is to assist the scientist after completing a fellowship and prior to the time he has demonstrated his ability as an independent investigator.

Grants-in-Aid.—These are awarded to scientists upon recommendation of the Committee on Growth of the National Research Council. Sixteen subcommittees representing the fields of biochemistry, biology, biopyhsics, chemotherapy, and clinical investigation aid in selecting the research to be supported. The work carried on by means of these grants-in-aid is presented.

Institutional Research Grants.—These are grants integrated with the cancer research program and for projects of special interest. There have been 35 such grants alloted since 1947. The number of workers involved in such projects in 1950 amounted to 1,100. The method of applying for these grants is outlined. It is pointed out that most research in this country supported by the American Cancer Society, the National Cancer Institute, the Atomic Energy Commission, and

various other foundations is largely supported by public funds. There have been 21 institutions aided by these grants, and there is a reliance placed upon the judgement of the institutions' authority which permits "fluidity" of application of these funds to particular phases of the stipulated investigation. There are 180 pages of brief reviews of research projects supported from July, 1949, to June, 1950. There is also a bibliography of 605 articles based on work supported in whole or part by the American Cancer Society and the names of the investigators and subjects under study supported by that Society from July 1, 1950, to June, 1951. A total of 254 such investigations have been granted the sum of $1,605,868.

Summaries of geographical distribution of various fellowships and the financial summary of the Committee on Growths recommendations to the American Cancer Society from July, 1945 to June, 1950 are also included.

Although lengthy, it is quite evident that both these reports have included only the essential aspects of the huge research program of the American Cancer Society. They are further documentary evidence of the progress medicine has made without governmental interference and are recommended reading for all interested in the administrative aspects of American scientific research.

Your Mind and Appearance. By Dr. Adolph Abraham Apton. Price, $3. Pp. 224, with 14 illustrations. The Citadel Press, 120 E. 25th St., New York 10, 1951.

As indicated by the title, this book stresses the psychic reaction of the patient to plastic surgery and to the plastic surgeon, rather than technical procedures. Deformities, congenital and acquired, are segregated and discussed in appropriate age groups.

The congenital malformations most commonly encountered during infancy and childhood are presented in some detail. This age group being particularly susceptible to burns, the author touches lightly upon the secondary contractures following such accidents. He brings out the psychologic development of this period and the frequently-encountered social withdrawal of such children from normal contacts.

The chapter on adolescence continues the development of the reaction of inferiority and inadequacy which begins during childhood and is particularly accentuated during this period of high sensitivity.

In the chapter on adulthood stress is placed on the sociological aspects of disfiguring scars, the relationship to employment and to social contacts. The author's wide experience enables him to draw upon many illustrative examples to emphasize the serious effect of a sense of inferiority, and the reaction of repulsion or disgust which crippled or disfigured individuals may feel are directed toward them. In many instances the variation is so slight that it may seem to the examining physician to be within normal limits, but to the patient the defect looms so large that the psychic maladjustment is by far the greater problem. Plastic and reconstructive surgery of this period has definite limitations, and there is special necessity for a sympathetic and understanding approach to the patient's problems, both physical and mental with the necessity for the utmost honesty and sincerity in describing the results which may be obtained, as well as in pointing out the impossibility of attaining perfection.

In discussing the aging period attention is drawn to the fact that the span of life has been definitely lengthened in the last few decades and the problems of this period have been correspondingly increased and multipled. Again emphasis is placed on the importance of a sympathetic approach and a thorough knowledge of the mental reactions characterizing this period.

A brief chapter is devoted to the contact of plastic surgeons with criminals, usually for the purpose of disguising features or removing marks of identification, but also for the purpose of changing the appearance of a released criminal so definitely that he may be able to regain a useful place in society. The opportunity of the plastic surgeon to relieve the sense of inferiority and enable the released prisoner to make a fresh start in life is a privilege which should be greatly prized and most carefully developed.

Other chapters dealing largely with psychology are devoted to the limitations of reconstructive surgery, modern aspects of plastic surgery, and proper screening of patients. The psychic reaction of the public toward malformed and disfigured persons, and the changed psychic reaction of the patient following plastic surgery make interesting reading. One chapter of definite value to the medical profession is that on "The Surgeon and the Patient," in which it is

particularly emphasized that the sympathetic understanding attitude of the surgeon is often more important than the technical procedures he uses, and the examiner is particularly warned against lightly brushing aside remarks of patients which, if followed carefully, will reveal the depth and intensity of some timidly expressed fears and reactions.

Many of the points which are stressed are well understood by all physicians interested in psychosomatic medicine and particularly by plastic surgeons. However, the book may be read with advantage by many practitioners who have occasion to see comparatively few deformed or disfigured persons. The psychic, psychological, and sociological aspects are emphasized throughout the book, but anyone seeking information regarding the technique of plastic surgery will be disappointed.

Regarding the photographs which occupy some 14 pages, the reader is reminded that many patients object to the use of actual photographs in a book which will be seen by the public. For that reason the author has had drawings made of the photographs which are rather close copies but evidently do not reproduce the photographs exactly. As the result of the artist's endeavors the end-results are probably nearer perfection than the eye of the camera would actually reveal. Also throughout the text there is a great multiplicity of letters reflecting the psychologic reactions of patients in greater or less detail. It would seem that the number of these letters could be definitely reduced without detracting from the value of the book, and the professional reader cannot escape the impression that the lay reader may believe that the results of plastic surgery are near perfection and absolute invisibility of scars, although the author has specifically warned against this on several occasions. The book is evidently intended mainly for the laiety, and as a result members of the medical profession may be confronted with quotations from it which will be colored by the interpretations of the lay mind.

Clinical Practice in Infectious Diseases. By E. H. R. Harries, M.D., and M. Mitman, M.D. Price, $6.50. Pp. 698, with 48 figures and 27 tables. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1952.

This is a very excellent text on infectious disease by a group of British authors. It was first published in 1940, and this represents the fourth edition. The book is divided in a general way into three parts dealing with the general problems of infection and epidemiology, separate chapters on the individual diseases, and a final group of chapters on the general management and control of infectious diseases. This is a particularly complete text with a total of almost 700 pages. All parts of the book are well done, but the clinical descriptions of the disease seem to be outstanding. Since this is a British book, the American reader may object to the slighting of some disease which are of particular interest to us. For example, the equine encephalitides and Rocky Mountain spotted fever are not at all adequately discussed in comparison with the other diesases. However, this is not any major fault. The authors have made rather good use of numerous line drawings showing the distribution of rashes and the clinical course of diseases. One can well criticize the selection of illustrations, however, for most of the color plates add little to the text. They are rather poor reproductions of color photographs of bacteria colonies, the normal throat, etc., and add nothing to the value.

In general this reviewer was quite favorably impressed with the text and can recommend it to students, physicians, and public health officers.

RX for Medical Writing. By Edwin P. Jordan and Willard C. Shepard. Price, $2.50. Pp. 103. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1952.

This is a book of 103 pages. Less than one-half deals with writing, the rest deals with economics of illustration, statistics, abbreviations, proof reader's marks, weights and measures, temperature equivalents, international atomic weights, and other useful but secondary material.

On the title page is the advice of Horace on the art of poetry: "Quidquid praecipies esto brevis." The authors do not mention him or obey him too well.

One of them, Jordan, takes responsibility for most of the book; Shepard, a medical artist, wrote the chapter on medical illustration.

The object of the book is to give some practical help to medical writers. In the first paragraph of the preface they say: "Good writing is one part inspiration and nine parts perspiration." They do not mention that Edison said this of genius.

We should expect a medical artist to have in mind the epigram of Michelangelo: "Trifles make perfection, and perfection is no trifle." This is the point they wish to drive home. They emphasize this in their advice on revision; there should be at least three revisions. Robert Louis Stevenson and William Osler spent more time on revision than on the first draft. If those masters of the art thought this necessary it is a good prescription for others.

If brevity is good in a book, it is better in a review. The authors prescribe for an age-old epidemic, the inability to write clearly. The disease attacks all classes, it is virulent among bureaucrats, sociologists, and medical writers. They offer a treatment which is not new, nor is it claimed to be, but if followed should be effective. It is modern and well presented.

Anyone who reads, marks, and inwardly digests what they offer should be benefited.

Penicillin in Severe Otorhinolaryngological Complications. A Symposium by Robert Lund and others. Price, $2.50. Pp. 120, with 27 figures. Ejnar Munksgaards Forlag, Nørregade 6, København, K., 1950.

This symposium represents a joint investigation of the treatment of otorhinolaryngological complications from the larger departments and clinics of Denmark, Norway and Sweden. Material consisted of the records of 421 patients who were treated with penicillin, of which 182 (45%) were submitted to bacteriological examination. Bacteriological data based on cultures from the primary focus were available in 16%, and from secondary complications in 19% of the cases.

The principal subdivisions in this symposium deal with bacteriological problems, and with the penicillin treatment of meningitis, tympanogenic labyrinthitis, otogenous and rhinogenous cerebral abscesses, petrositis, osteomyelitis, tonsillogenic and otogenic thrombophlebitis, and sepsis. Allergy and incidental toxic effects are covered in the final chapter. Each chapter contains an excellent résumé of the literature, in addition to analyses of the material studied by the authors.

There is such a wealth of information in this pamphlet that a summary could not do justice to the contribution. It should be read by all who might erroneously believe that antibiotics and chemotherapy have eliminated otorhinologic complications. The role of surgery, modified somewhat by the advent of these agents, is every bit as important as formerly, and carries the added obligation of more complete understanding of the uses and limitations of the drugs. Certainly the notation of a 33% mortality rate in (otogenic) pneumococcus meningitis and a 31% mortality in Streptococcus meningitis still present a challenge to physicians who see and treat such conditions. The same might be said of brain abscesses resulting from sinus or ear complications. Otolaryngologists in particular will find this book a stimulating and valuable addition to their libraries.

Clinical Pediatric Urology. Meredith Campbell, M.S., M.D., F.A.C.S., with A Section on Nephritis and Allied Diseases in Infancy and Childhood. By Elvira Goettsch, M.D. and John D. Lyttle, M.D. Price, $18. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; W. B. Saunders Company, Ltd., 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1951.

This is the most comprehensive book which has appeared on pediatric urology in many years. The author's long interest in children's urinary diseases, coupled with voluminous material, has made such a volume possible. The average urological practice does not yield the experience which the author possesses.

Approximately one-sixth of the book is devoted to examination and diagnosis. Noteworthy are normal values of fluid balance at various ages of infancy and childhood. Also included is an excellent exposition of the many recent additions in diagnostic procedures. New type cystoscopes are reviewed. Many excellent reproductions of urograms are used to demonstrate the nature of the various types of uropathy.

The embryology of the urinary tract is closely correlated with all known anomalies of the urinary tract. And since congenital defects and anomalies are frequently the cause of urologic disease in the newborn and the infant, this portion of the book is helpful in undertaking the treatment of these defects.

Urinary infection, a common finding in children, is thoroughly covered, not only as to etiology but also as to prevention and treatment. There is an excellent review of the usefulness of the antibiotics together with dosages to be used on children.

Diseases of the genitalia in both sexes have been included. Various criteria for the early determination of sex in doubtful children are thoroughly explained and demonstrated. Included here are the values of cystoscopic examination and surgical exploration.

Chapters on calculus disease, obstructive uropathy, and tumors discuss the peculiarities incident to children and infants.

The newer physiology of the adrenal glands and its application to abnormal syndromes, which affect the growth, sex, and skeletal structures of children, is included.

There is likewise a detailed exposition of surgical procedures in children, and various standard operations are well illustrated.

A short résumé of nephritis and allied diseases is also included, since not infrequently such diseases must be integrated with urologic diagnosis.

Such a book is a necesssity for the practising pediatrician and urologist. It is only by early recognition of urinary disease in infancy that corrective procedures will be of life-saving value.

The author is to be commended for this large and useful contribution to urology and pediatrics.

Antibiotic Therapy. By Henry Welch, Ph.D., and Charles N. Lewis, M.D. Price, $10. Pp. 549, with 7 illustrations. The Arundel Press, Inc., 3801 Connecticut Ave., N.W., Washington, D. C., 1951.

The first nine chapters of this book deal with the isolation of antibiotics and present the antimicrobial activity, pharmacology, and dosage forms in useful and informative fashion. Numerous useful charts help the reader to evaluate various methods of antibiotic therapy and make comparisons between oral, intravenous, and intramuscular routes of administration. In this age of antibiotic medicine, it behooves all physicians to be familiar with the pharmacology of the various agents used, and this volume is an excellent source of such information.

The last 11 chapters discuss the treatment of specific infections. The material is presented as a rather extensive review of the literature with excellent lists of references. The reader must evaluate in his own mind the drug of choice after analyzing the numerous reports presented in each section. The reviewer feels that the book would be more practical if the authors would make more specific statements, perhaps in a summary at the end of each section, regarding the most valuable agent in a specific type of infection.

In discussing amebiasis the statement is made that emetine hydrochloride is the most valuable drug for treating hepatic involvement. This statement is open to question since no mention is made of chloroquine. Under tuberculosis, streptomycin is discussed at length with no reference to dihydrostreptomycin. The statement is also made that streptomycin should not be used in the general treatment of tuberculosis if other therapeutic measures are effective. This would not agree with the opinion of many students of this disease.

This book represents an extensive amount of work by the authors and may well be recommended as a source book for information on antibiotic therapy.

La Pratique des déviations vertébrales: scoliose, cyphose, lordose. Edition 2. By C. Roederer and R. Ledent. Price, 1700 French francs. Pp. 338, with 233 illustrations. Gaston Doin & Cie, 8, Place de l'Odéon, Paris, 6e, 1951.

This is a second edition which contains considerable revision of the original text. The first 284 pages of this volume are concerned with a discussion of the anatomy and physiology of the spine and the etiology, pathology, and treatment of scoliosis. Chapter 18 deals with the problem of round back and kyphosis of adolescence, and there is a short chapter on lordosis.

Theories of etiology as expressed in this volume are similar to those which have been found in the literature of the past 50 or 60 years. The treatment recommended is essentially the same as that which was standard among orthopedic surgeons in this country prior to about 1920. The authors emphasize the importance of prophylaxis through carefully supervised and planned

gymnastic exercises to prevent scoliosis or to correct it at its very inception. The exercises and physical therapy which they recommend and illustrate with adequate line drawings are not essentially different from those which were recommended by Steindler and were used widely by orthopedic surgeons throughout this hemisphere until about 1935. In addition to the exercises, which include various types of stretching to lengthen shortened spinal muscles, the authors have described body jackets and retention appliances. These, too, are similar to the casts and body jackets recommended by Abbott, Goldthwait, Taylor, and other orthopedic surgeons early in this century. Almost without exception, orthopedic surgeons, in the United States at least, have long since abandoned hope of correcting structural deformities of the spine or of preventing further progress of these deformities by means of any type of physical therapy or exercise program, with or without the use of body casts, jackets, or braces. Scoliosis and kyphosis are still unsolved problems in orthopedic surgery. The most gratifying results in the treatment of scoliosis in the United States have been obtained by means of correction of the spine by combinations of traction, turnbuckle casts of the type proposed and used by Risser, or modifications of this method and arthrodesis of the corrected scoliotic curvature.

This book constitutes a well-written and well-illustrated review of the history of methods used in the treatment of deformities of the spine, and is of interest principally from that standpoint. For the most part, the methods described for treatment have long been out of date and supplanted by methods which have been more successful in the hands of the average American orthopedic surgeon. Earlier recognition of beginning lateral curvatures of the spine and institution of vigorous gymnastic exercises, such as proposed by these authors, would be worthwhile and would no doubt make unnecessary some of the forced corrections and spinal fusions which have become rather uniform practice among orthopedic surgeons of this hemisphere.

Your Diabetes: A Manual for the Patient. Edition 2. By Herbert Pollack, M.D., and Mary V. Krause, M.S. Price, $3. Pp. 212. Paul B. Hoeber, Inc., 49 E. 33d St., New York 16, 1951.

This is a second edition of a very good diabetic manual for the patient. It has one of the most interesting historical chapters of any book for the patient. Considerable time is spent discussing the newer insulins, the way they are handled, and the particular techniques for each. Chapters on juvenile and adolescent diabetics, pregnancy and diabetes, and the diet for infants and children are excellent. Considerable discussion is given to the psychosomatic side of diabetes. Chapters on the diet have been adapted from "The Diabetes Guidebook for the Physician" published by the American Diabetes Association, and embrace the newest food exchange system of diet control. There is also a question-and-answer chapter at the very end of the book.

Year Book of Pediatrics, 1951. Edited by Henry G. Poncher, M.D., and Julius Richmond, M.D. Price, $5. Pp. 441. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1951.

The 1951 Year Book continues the tradition of previous volumes in presenting the best of current literature in abstract form. The editors' comments interpret the application of the abstracted information and pediatric practice. Introductory editorials head specific chapters, providing information regarding latest developments, trends, summaries, reorientation, and critical comments. The editorial policy makes the book far more than a compendium of current abstracts; it becomes an intructive discriminating seminar. The practicing pediatrician should not be without this book.

Pharmacology in Clinical Practice. By Harry Beckman. Price, $12.50. Pp. 839, with 152 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1952.

This book supplants the old and familiar Beckman's "Treatment In General Practice." Why the form and treatment of the book should have been changed is not clear. The author states that he is thinking in terms of specific disease, in terms of symptoms, and not of anatomical groupings of organs or chemical groupings of drugs. The book is thus divided into two

sections. Section one presents the pharmacological aspects of nearly all the major problems that arise in medicine and dentistry. Section two is a listing of all the drugs mentioned in section one, with a few chemical and physical properties of these drugs.

As regards the pharmacology involved in the text, it can only be said to be minimal, and the book would have better been titled "Therapeutics in Clinical Practice." The content as regards drugs currently used is up-to-date and complete. An effort is made to divide the text into sections covering most of the fields of medical practice. Some of these are exhaustively covered, for example 100 pages on cardiology; others are sketchy and some topics are mentioned only to be dismissed. The section on pediatrics is completely useless and even, in one case, decidedly harmful where it is stated that it is rational to give sedatives at bedtime to children prone to have croup. No mention of therapy is made, other than syrup of ipecac and the statement that increasing the humidity of the bedroom may be helpful.

For the physician wishing to find quickly the treatment for a given condition the book will undoubtedly be useful. The breezy and whimsical statements found scattered throughout the text do not lend dignity to the volume. They should be deleted.

The Child in Health and Disease. Edition 2. Edited by C. G. Grulee and R. C. Eley. Price, $15. Pp. 1255, with 319 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1952.

The authors have succeeded in revising and incorporating new and authoritative material in this second edition of "The Child in Health and Disease."

Besides representing a very distinct addition to the textbook field in pediatrics, they have crystallized for practical use the new knowledge which has emerged from medical investigation. Their ultimate goal in the presentation of material for the proper training of the medical student plus a volume that the man who carries the little black bag could use in his practical bedside application has been reached. It is difficult to understand how any conscientious pediatrician or general practitioner can avoid using this book in his daily work.

The second edition contains many new names among the 87 collaborators. The book has been completely rewritten. The contributors to this work have been carefully and wisely chosen.

Chapters concerning adoption, medical supervision of summer camps, cardiovascular surgery, viral hepatitis, erythroblastosis, and pancreatic fibrosis have been added. Latest developments in the field of therapy with antibiotics are incorporated including the use of penicillin, streptomycin, aureomycin, oxytetracycline ("terramycin"), chloramphenicol, and others. The action and uses of corticotropin (ACTH) and cortisone are explained.

The book is admirably written throughout and very easy to read. The index is most complete and, as a one-volume reference book, it meets a need.

Attaining Manhood. By George W. Corner, M.D. Price, $1.50. Pp. 97, with 16 illustrations. Harper & Brothers, 49 E. 33d St., New York 16, 1952.

Attaining Womanhood. By George W. Corner, M.D. Price, $1.50. Pp. 112, with 15 illustrations. Harper & Brothers, 49 E. 33d St., New York 16, 1952.

These companion volumes, written by the distinguished director of the department of embryology of the Carnegie Institute of Washington, are perhaps best reviewed together. The author's long study and experience have been very effectively translated into these volumes for lay readers.

The factual information and illustrations are excellent and parallel in both volumes. Biological information is amplified by an intelligent presentation of emotional, social, and cultural aspects of sexual matters. The language and style of presentation limit the usability of the volume largely to high school and college students. The presentation is sufficiently mature to render the volumes useful to adult groups as well. Parents, teachers, and all other people caring for children should have as a minimum the background of information provided by the author.

The reviewer has some question concerning the advisability of presenting this information in two separate volumes. Since much of the material is paralleled or is identical in the companion volume, it would seem more logical to combine the two.

Physicians in particular should find these volumes useful in education work with individual children and parents. In addition they can be helpful as references for physicians who are called upon to participate in educational activities concerning sex in the community.

Approved Laboratory Technique. Edition 5. By J. A. Kollner, E. N. Spaulding, and H. W. Robertson. Price, $12. Pp. 1,180, with 431 illustrations. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York 1, 1951.

"Approved Laboratory Technique" is an excellent reference text, which is designed to be of equal usefulness to medical student, graduate physician, and laboratory worker. Descriptions of individual procedures are simple and succinct, but include discussion of principles involved, calculation of results, collection of suitable specimens, and important sources of error. Whether one is interested in the care of technical equipment, the preparation of glassware, the health of experimental animals, or the preservation of pathological specimens, useful information adequately indexed is available. From the standpoint of the pediatrician, it is regrettable that micromethods are not included. The context is generously seeded with well-conceived charts of practical information, but although the majority of photographic plates are good, the reviewer is disappointed by a considerable number of illustrations. The inclusion of key bibliographic references in some chapters is highly desirable; however, their absence in other sections of the book will detract from its value in the minds of some readers. In isolated instances indexing leaves something to be desired. For example, such a commonly-used procedure as the five-tube sugar determination on spinal fluid is not listed in the index, though it is covered under the subject of influenzal meningitis.

In summary, well-organized and well-presented subject material, contributed by a distinguished group of collaborators, far outweighs any minor objections which can be raised.

CORRECTION

The next meeting of the American Academy of Pediatrics will be in Miami, Fla., from Oct. 6 to 9. The time and place of this meeting were incorrectly given in the Directory of Pediatric Societies, published in the January and April issues.

In the October, 1952, issue, page 511, the correct address of Dr. Allen J. Hill Jr. should be as follows: Department of Pediatrics, University of Oregon Medical School, 3181 S. W. Sam Jackson Park Rd., Portland 1, Ore.

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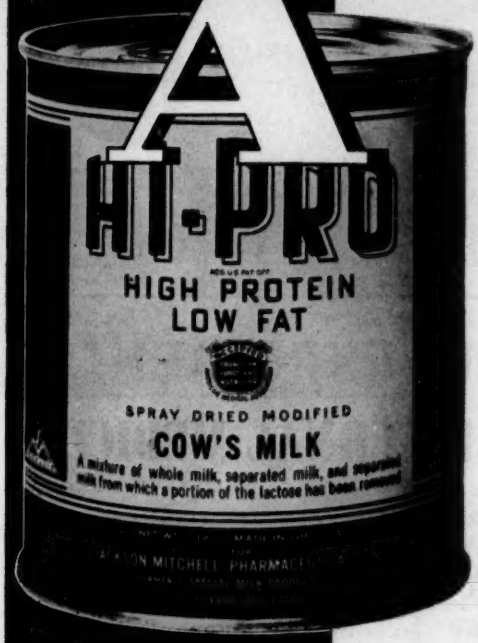
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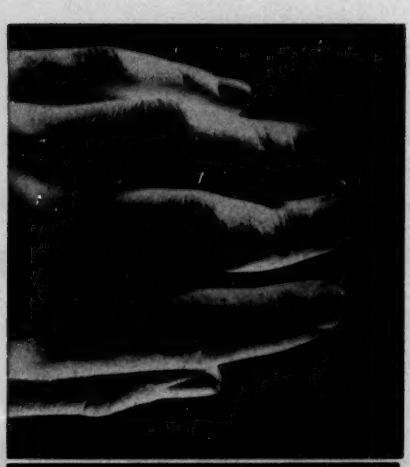

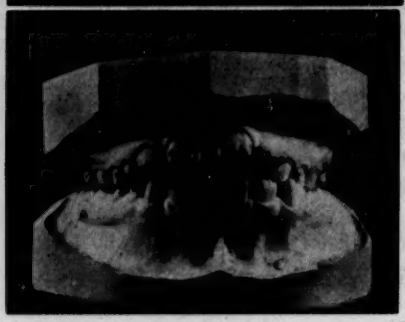

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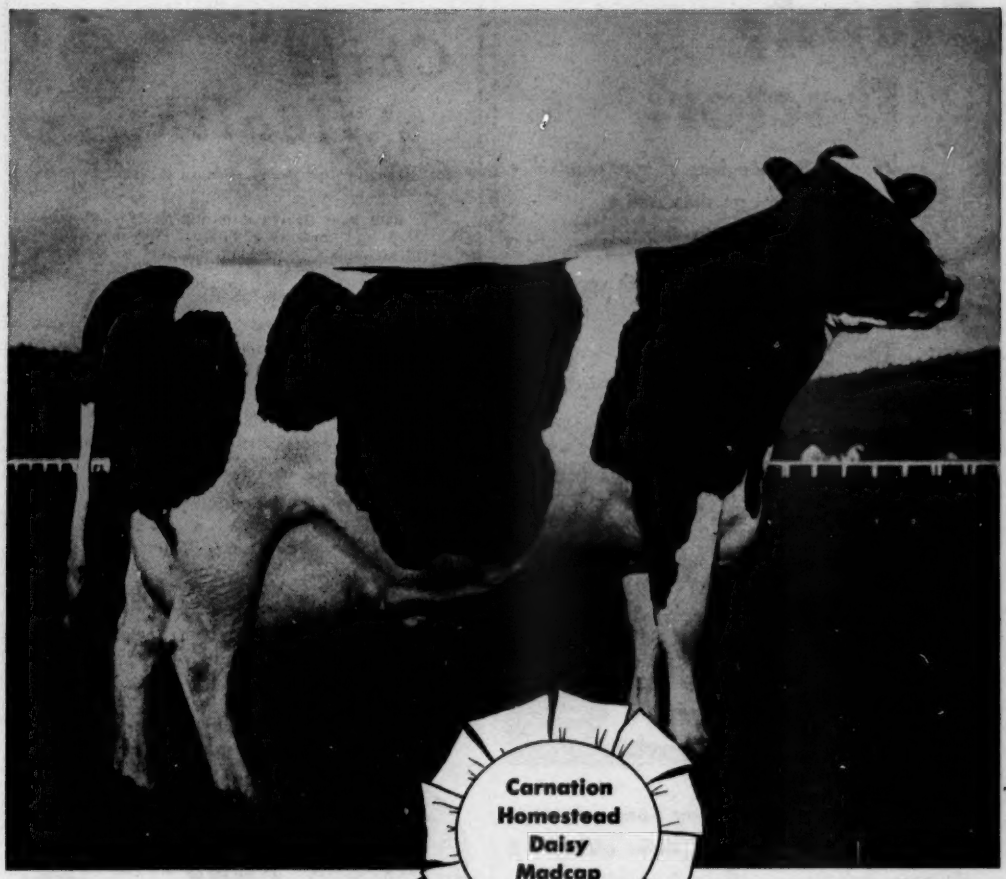

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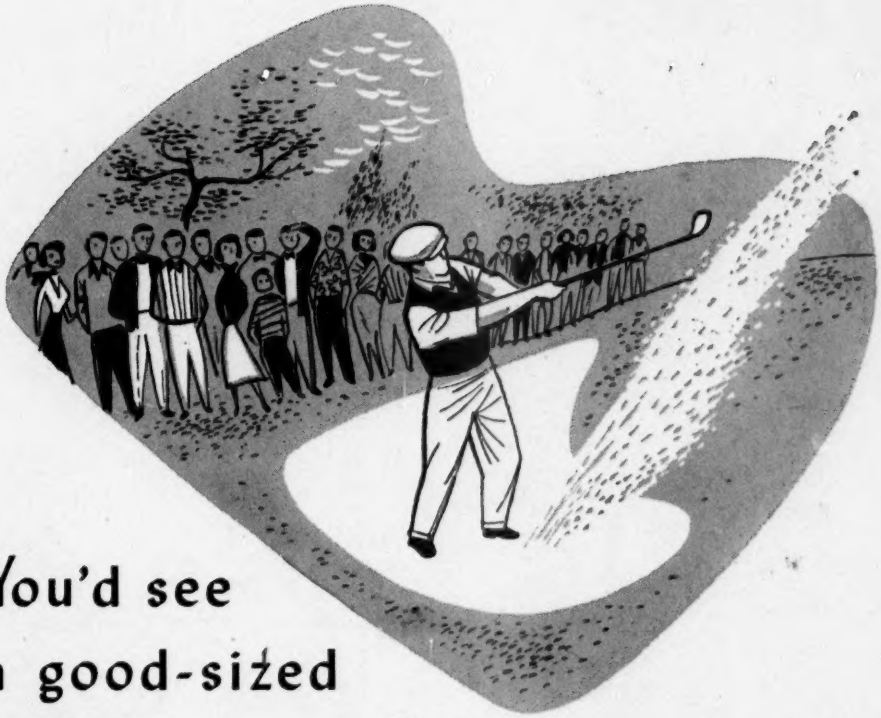

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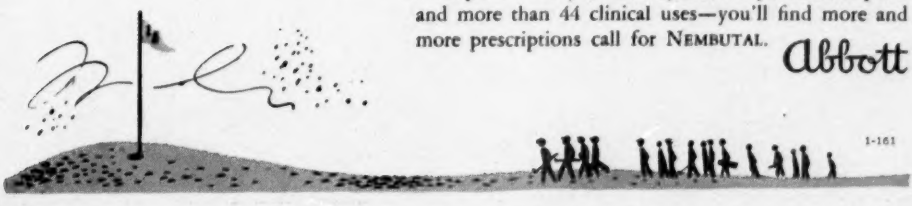

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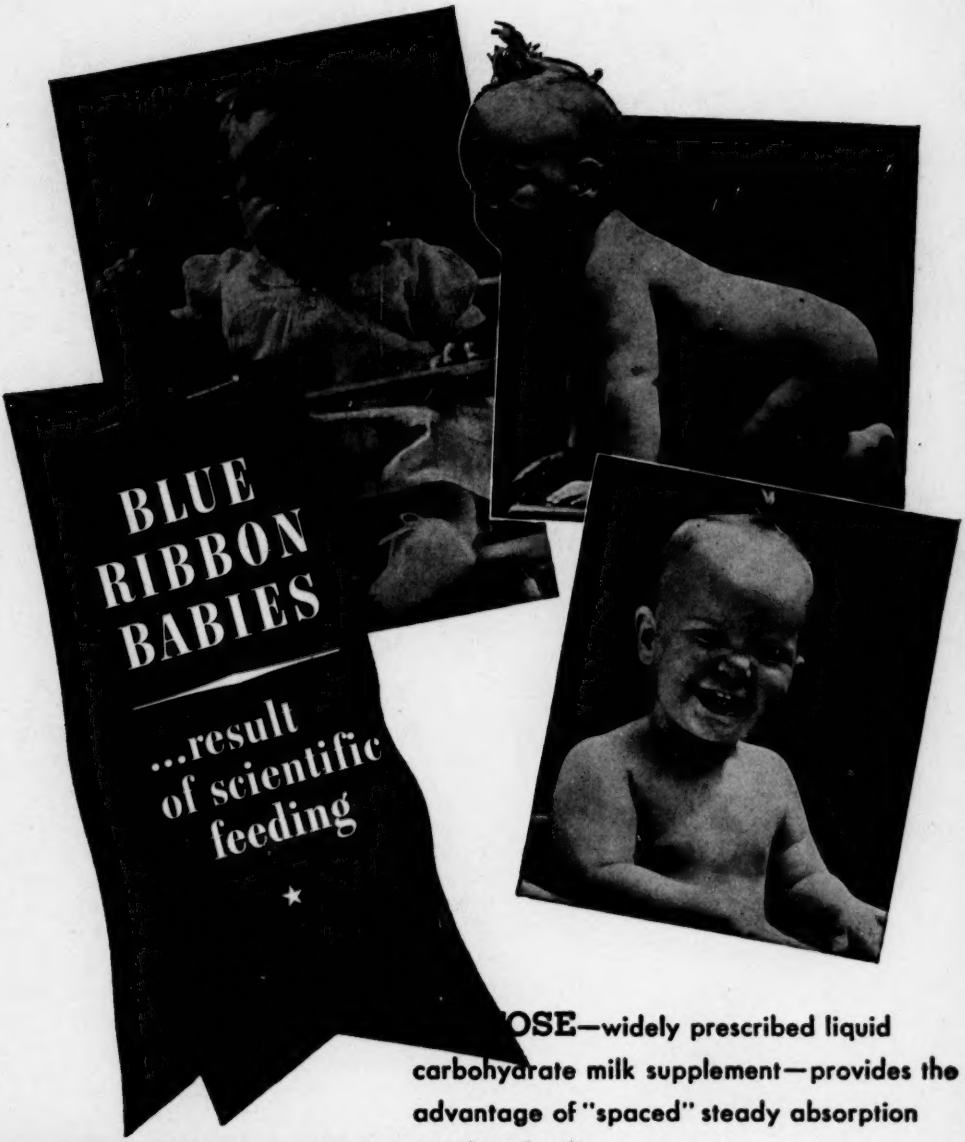

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